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FOOD SAFETY AMENDMENTS OF 1989

HEARING

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

ONE HUNDRED FIRST CONGRESS

FIRST SESSION

ON

S. 722

TO AMEND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT TO REVISE THE AUTHORITY UNDER THAT ACT TO REGULATE PESTICIDE CHEMICAL RESIDUES IN FOOD

JUNE 6, 1989

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FOOD SAFETY AMENDMENTS OF 1989

TUESDAY, JUNE 6, 1989

U.S. SENATE,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
Washington, DC.

The committee met, pursuant to notice, at 9:46 a.m., in room SD-430, Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the committee) presiding.

Present: Senators Kennedy, Harkin, Hatch and Cochran.

OPENING STATEMENT OF SENATOR KENNEDY

The CHAIRMAN. The committee will come to order.

Our hearing today addresses an important public health issue, the safety of the U.S. food supply. The measure before us, the Food Safety Amendments of 1989, will enhance Federal oversight of the use of dangerous pesticides in the Nation's food supply and provide greater assurance that the foods we eat are safe.

Citizens across the country are becoming increasingly concerned about this issue. Recent reports of the danger to children from the use of cancer-causing pesticides on apples have raised serious questions about the benefits and the risks of these chemicals. The scare over Chilean grapes raises questions about the extent of food inspection by the Federal Government. The Federal Government is not doing enough to assure the public of the safety of the fruits, vegetables, meats and fish that we eat. The people no longer accept assurances of "Trust us," either from the pesticide and chemical companies or from the Federal Government.

Pesticides and other chemicals are commonly used by farmers to protect crops from infestation. These products have significantly improved crop yield and productivity, but at what expense to the health of our citizens? Many pesticides known to cause cancer and other adverse health conditions are commonly used in agriculture. Under current law, the two Federal agencies charged with the task of assuring the safety of the food supply and protecting the public health—the Environmental Protection Agency and the Food and Drug Administration—permit the use of these dangerous chemicals. To respond to the real and justifiable concerns about the safety of our food supply, we need to strengthen the authority of these agencies to limit pesticide and other chemical residues on food, and remove from the marketplace chemicals known to cause serious adverse health effects.

Reports from Government and the private sector underscore the growing concern. In 1987, the National Academy of Sciences reported that the legal use of 28 pesticides studied could lead to cancer in up to one out of every thousand people exposed. The Environmental Protection Agency has identified at least 25 other carcinogenic pesticides legally used on food.

Earlier this year, the Natural Resources Defense Council issued a report called "Intolerable Risk: Pesticides in Our Children's Food," which provided evidence of the risk of cancer in children. In 1986, the General Accounting Office reported that the current pesticide-monitoring techniques used by the Food and Drug Administration can identify only 40 percent of the pesticides which the agency classifies as posing moderate to high health risk. The Environmental Protection Agency has statutory responsibility for establishing limits on the allowable concentration of pesticides in food. However, EPA's so-called common-sense approach toward cancer-causing pesticides and chemical residues is poorly defined. The risk/benefit standard under which the agency prefers to regulate allows a small risk of cancer which runs counter to the zero tolerance cancer prevention policy applicable in other areas of the law.

In addition, the current calculation of negligible risk does not take into account the total consumption of various food products for specific population groups and does not consider inert ingredients. That is why we need to strengthen the statutory requirements. Determinations of safety must be based on sound science, not anecdotes or emotion. The challenge we face in Congress is to ensure that legal food is safe food.

The Food Safety Amendments provide a comprehensive revision of EPA's current authority to set tolerances for pesticides that may remain in food. The bill incorporates many of EPA's current practices but also establishes certain fundamental reforms recommended by the National Academy of Science. One of the most important provisions establishes a negligible risk standard for pesticides consistent with the rules for food additives and color additives and environmental contaminants. Residue of pesticides and chemicals in food must have a negligible risk of causing adverse human health effects in groups such as infants and children.

In many other areas, we have been able to achieve a realistic reconciliation of the interests of public health, farmers, the food industry, and chemical companies. There is no fundamental inconsistency between these interests. The food industries can only thrive when the public has full confidence in the quality and safety of the food supply. I look forward to the comments from today's witnesses and to their recommendations on this legislation.

We welcome back to our committee Frank Young, the commissioner of the Food and Drug Administration; Victor Kimm, who is the acting assistant administrator for the Office of Pesticides and Toxic Substances of the Environmental Protection Agency; and Jack Parnell, deputy secretary, Department of Agriculture.

We look forward to your testimony. Dr. Young, we appreciate your willingness to join us this morning.

STATEMENTS OF FRANK E. YOUNG, M.D., Ph.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ROCKVILLE, MD; VICTOR J. KIMM, ACTING ASSISTANT ADMINISTRATOR, OFFICE OF PESTICIDES AND TOXIC SUBSTANCES, U.S. ENVIRONMENTAL PROTECTION AGENCY, WASHINGTON, DC; AND JACK C. PARNELL, DEPUTY SECRETARY, U.S. DEPARTMENT OF AGRICULTURE, WASHINGTON, DC

Dr. YOUNG. Thank you very much, Mr. Chairman, for calling this hearing. I think it is an important one because there has been a great deal of apprehension in regards to food safety. Thus, this type of hearing really brings forward the facts and enables us to work together toward meeting this goal.

In order to provide time for questions, I will only focus on a few very brief issues, and if my statement could be introduced to the record.

The CHAIRMAN. Your statement will be included in its entirety, as if read, in the record.

Dr. YOUNG. Thank you.

I would like to focus first on the concept of a risk, a minimal risk, an acceptable risk, that is raised in this bill. First of all, I think that this is the right step. As science has progressed, we have been able to determine and detect compounds much more readily than we could in the early 1950's. I think second that this type of an identification should be made over the entire food supply, so that rather than just merely looking at pesticides and moving them out from under the so-called Delaney clause and dealing with "The Delaney Paradox," I would recommend that it would be important to look at other things, such as color additives and food additives, as you finally analyze this bill.

I would also think that it is important to focus on the topic, as you have, of using the one in a million upper-bound risk. That is a good number, a sound number at this time. But I would urge that as you finally put the bill together that you might want to give some flexibility because science has progressed; and when we revisit this 10 years from now, I am sure we would want to have the right number and allow, just as you said in your opening, the scientific standards to determine what is negligible risk. And I believe by possibly stating that one has a contemporary upper-bound risk of one in a million, but in the future there might be further scientific advances, one would cover that.

We also feel that once the risk is established, the tolerances set, that it is important to have the appropriate amount of compliance testing. And in this sense, we feel that it is important to the public to have a somewhat larger testing program than is underway today. We would also like to have that testing program not only be the testing program that is done under the aegis of the Food and Drug Administration, but also combine State data so that we can utilize work that is done in many States to build a concerted picture, and also have access to some of the manufacturers' testing data so that we could use that as well. We feel by building compliances higher and doing a swifter job on some of the tolerance——

The CHAIRMAN. Let me just ask you about the information now made available by the industry. Are you satisfied that you are able to obtain sufficient information under current law?

Dr. YOUNG. We believe that we can get through a cooperative approach enough of the information under the current law, and we have developed a program that I will submit for the record, which tries to integrate this. But we do feel that the back-up assay by the Food and Drug Administration provides a validation test. I would not want to go out on the industrial data alone; to not have an appropriate level of testing would make that difficult.

I would also like to submit for the record an analysis that we did on just looking at raw apples for pesticides. I was surprised to find out that there are a hundred different pesticides used in apples. And if we were to just look at the pesticides alone and make a statistical sample rather than a sufficient sample, one would have a cost for just that one crop of almost $50 million. So how to design the appropriate testing program is very important, and I would like to give you those analyses for the record.

[The analyses of Dr. Young follow:]

Cost Estimate for a Comprehensive, Statistically Based Analysis of Raw Apples for Pesticide Residues

April 25, 1989

The Food and Drug Administration's pesticide program currently samples and analyzes some 18,000 food shipments each year to enforce pesticide residue tolerances established by the Environmental Protection Agency. The current sampling approach combines a random sampling component ("surveillance sampling") where there is no suspicion of a pesticide residue problem, and a directed sampling component ("compliance sampling"), which is utilized as follow-up to violations uncovered by surveillance sampling or where information suggests a possible problem. Historically, FDA has sampled less than 1 percent of the individual shipments of foods for pesticides.

Because of the large numbers of food types and shipments, and the limited resources available to FDA for pesticide residue monitoring, the Agency has not attempted to implement a "statistically based" sampling scheme, recognizing that the available Agency resources were insufficient to handle the large number of collections and analyses that such a scheme would entail. Nevertheless, the Agency is now exploring the possibility of developing under contract a model for a statistically based sampling plan which would provide FDA with a series of options on which to base its sampling and analysis approach.

To illustrate the magnitude of a statistically based effort, following is a brief summary of the resources that would be required for sampling and analysis of domestic and imported fresh apples to accomplish: (1) sampling/analysis of all U.S. producing farms and all import entries; (2) sampling/analysis of a statistically based cross section of the fresh apple supply; and (3) approximate what a similar effort might cost (personnel and funds) if extrapolated to the entire food supply. The following summarizes the Agency's estimates.

Question: What resources—both time and funds—would be required for FDA laboratory analysis of raw applies for all 100 pesticide residues with EPA tolerances? (processed apple products not considered)

"Complete" Single Sample Analyses:

Tolerances exist for residues of about 100 pesticides on apples. About 50 of these pesticides may be determined by FDA using two of the Agency's multiresidue (or efficient, "multiple pesticide") analytical methods. The multiresidue methods require about 4-8 person hours per sample. so, for these 50 of the 100 pesticides, laboratory analysis would require a total of about 2 person days per sample. Because of their chemical properties, the remaining 50 pesticide residues cannot be determined using these multiresidue methods. Instead, analysis using less efficient single-residue methodology is required. Analysis for these 50 pesticide residues in a single sample would require that FDA use about 40 separate analytical methods, each capable of determining only one (or at most, a few) residues. Each single-residue method requires about 16 person hours (2 person days). Thus, analyses for all of these 50 pesticides would require 80 person days.

In summary, collection and analysis of a single sample of apples for all of the approximately 100 pesticides with EPA tolerances would require about 82 person days and $33,000, based on a cost of 1 person year at $100,000.

Sampling and Analyses of all Apple Shipments U.S. *(domestic and imported)*:

There are tens of thousands of domestic and imported apple shipments annually (processed apple products excluded). According to United States Customs food import figures for 1987, there were about 3,000 "formal" import entries. Domestic shipments may be conservatively estimated using USDA's 1982 crop statistics for "harvested" farms at 24,000/year. Thus, the total number of domestic and imported fresh apple shipments is about 27,000/year. Sampling and analysis of each shipment for residues of all pesticides with tolerances would therefore require expenditure of about $900 million (2,200,000 chemist person days).

Statistically Based Pesticide Residue Profile of U.S. Raw Apple Supply *(domestic and imported)*:

In FY 87 and 88, the pesticide violation rate for apples, based on FDA's results, was 0.23 percent. Assuming a somewhat higher violative rate of 1 percent, FDA would need to randomly sample approximately 1,500 of the estimated 27,000 (domestic plus import) shipments of fresh apples to be 95 percent confident that no more than 1.5 percent would exceed EPA tolerances. (This is based on finding that the actual violative rate for the 1,500 shipments is no more than 1 percent.) This level of effort represents about 5.5 percent of the 27,000 raw apple shipments. Thus, nearly $50 million would be required to fund this level of effort.

Summary/Conclusion

It is apparent that implementation of a pesticide monitoring program encompassing either (1) "total" sampling and comprehensive analyses of all shipments of fresh apples for all pesticides with EPA tolerances, or (2) conducting a statistically based total pesticide residue profile for fresh apple would exceed FDA's current resource allocation for its pesticide monitoring program. Of course, if all processed apple products were considered, the figures would increase dramatically.

If either of these approaches were extended to all foods under FDA's jurisdiction (about 125 different crops (domestic and import), not including the many different varieties of each crop), the increase in monitoring cost would be substantial. While there are not always as many EPA tolerances for each of these crops as the 100 that exist for apples, one might reasonably assume that the total cost to conduct a similar statistically based study for all crops would amount to 50 to 100 times that calculated for apples.

The **Chairman**. Let me understand. You are saying just to test the various pesticides for apples would cost you $50 million?

Dr. **Young**. What we did was to look at, in this particular case, a statistical sample, and there is a very great difference between dealing with a statistical sample and a representative sample. One of the problems with testing that has led to confusion is that a lot of the rhetoric in public was that we need to have a statistically valid sample, and I think that is inappropriate. We need to have a representative sample.

We did the calculations to show that if you did a statistical sample, it would be that high; however, if we do a representative sampling, with FDA, States, and industry, we believe that that is a manageable number, and we can present figures on that as well.

Finally, I would like to say that I strongly support the review of the inert compounds, as you mentioned, but I would develop the strategy, just as EPA is, of looking at the most significant inerts, and making it a hierarchical approach so that we look at the most significant compounds from a public health standpoint, and then later look at any others. To do an interaction among pesticides, as was suggested in the bill, would be extraordinarily difficult. The apple survey shows that, because right now we do not have the methodology scientifically to really study the interaction between those. I will also submit for the record one comprehensive risk assessment that we did on some food additives to show you just what it takes to do six food additives from a risk assessment.

Dr. YOUNG. In deference to your time, sir, I would like to stick to the five minutes and then answer any questions that I could at a later time. But these points are comprehensively discussed in the testimony.

[The prepared statement of Dr. Young, risk assessment referred to, and questions and answers by Senator Kennedy and Senator Hatch follow:]

PREPARED STATEMENT OF FRANK E. YOUNG

Mr. Chairman:

I appreciate the opportunity to testify today on S. 722, the "Food Safety Amendments of 1989." This legislation would revise the authority of the Environmental Protection Agency (EPA) under the Federal Food, Drug, and Cosmetic (FDC) Act to regulate pesticide residues in food. The bill would also have both a direct and indirect impact on the Food and Drug Administration (FDA).

BACKGROUND

This hearing is especially timely in view of the recent controversy surrounding the pesticide Alar, and the intensity of public interest and concern about the use of pesticides generally. We are taking these concerns very seriously. Indeed, in order to better understand the public's perspective on this issue, last month I chaired a meeting with representatives from sixteen consumer organizations to discuss the confusion engendered by the Alar incident and public perceptions of risk. Representatives from EPA and the Department of Agriculture also participated. The message we received was strong and clear: people are upset about pesticides because the risks, relative risks, and the benefits of pesticide use are not completely known or understood.

In the case of Alar, many people were shocked by reports that some degree of risk might even exist. The situation was further confused when the data and conclusions of public and private experts did not agree. It was not suprising, then, that FDA was inundated by calls from consumers, asking whether apples were or were not safe to eat. EPA can probably recount similar experiences.

The Alar controversy highlighted certain issues for us. First, it demonstrated that the government needs to do a better job of explaining relative risks to the American people. Second, we need to build greater public trust in Government. This requires, at the very least, ensuring that the statutory framework for pesticide regulation is consistent, sensible, and enforceable, and provides Federal agencies with adequate tools to do the job.

Benefits to Consumers vs. Relative Risk

Clearly these responsibilities will continue in the foreseeable future. Although there is growing interest in farming practices which allow decreased use of pesticides, at the present time, there is no efficient way to produce crops on a large scale without pesticides since large scale crop production inevitably results in concentration of insects and other pests. Likewise, the American public has come to expect that fresh, high quality, attractive, and wholesome fruits and vegetables will be readily available, year-round, at reasonable cost. Much of our produce, however, is grown in other States or countries and transported great distances. The availability of these products depends on the use of both pre- and post-harvest pesticides. Without the use of these pesticides, many raw fruits and vegetables could not withstand the rigors of handling, transport, and storage, and still appear fresh and appealing to consumers at the time of purchase.

These benefits to consumers, of course, must be weighed against the risks to humans and the environment, and the results of this evaluation process must be effectively communicated and understood. The public must understand that most pesticides are, by their very nature, toxic substances. It is unlikely that a highly selective chemical pesticide that would affect only its intended target will ever be created. In short, the perfect pesticide will probably never be found.

FDA has long been involved with the regulation of substances that provide great benefits but also have various toxicities associated with them, and we are quite familiar with the chemistry and toxicity of pesticides. Until 1970 when EPA was created, FDA periodically bore the responsibility for setting pesticide tolerances, in addition to enforcing the levels of pesticide residues found in foods. Some of the earliest pesticides used were lead arsenate and nicotine, and much of the Agency's early research and regulatory resources were used to control lead residues caused by spraying lead arsenate on fruits and vegetables.

Pesticides came into widespread use following DDT's success during World War II in controlling flies, lice and other disease carrying pests. As the use of these new pesticides grew, it became evident that these compounds could affect not only the pest they were intended to control, but also man and the environment. Some, including DDT, were found to persist in the environment for many years. A comprehensive regulatory approach to pesticides became essential.

We know that this approach requires a sound premarket approval process and scientifically defensible tolerances, based on concepts that people can understand and trust. It must include inspection, analytical, enforcement, and educational programs that are adequate for the job. In addition, mechanisms must be available for cancellation of pesticide uses without creating major disruptions of the food supply or needlessly causing public alarm.

Nevertheless, we also know that even the very best possible system can never be a guarantor of absolute safety. As long as chemicals are used in agriculture, the potential for risk will be present. The role of Federal agencies must be to assure relative safety by evaluating the risks of pesticides, setting safe limits for residues, and enforcing these limits. Through proper risk assessment and management, risks can be reduced to insignificant, or "negligible" levels.

NEGLIGIBLE RISK/DELANEY CLAUSE

Although FDA believes certain provisions in this bill would improve pesticide regulation, we have serious concerns about the remainder of the bill due to the problems described below. The bill, however, is a step in the right direction because it applies the concept of negligible risk to pesticides and recognizes the need for a consistent standard in regulating pesticide residues in both raw agricultural commodities and processed foods.

As you know, pesticides which are applied to or concentrate in processed foods are subject to the Delaney clause in the law, while pesticides in raw agricultural commodities are not. The Delaney clause has been interpreted as requiring absolute safety, in that even negligible quantities of a carcinogen are prohibited. At the time the clause was first enacted, over thirty years ago, an absolute interpretation of the Delaney clause was consistent with the scientific knowledge of the day.

"Negligible risk," on the other hand, is defined in the bill as a risk of harm that is less than one in a million, and that is not likely to cause or contribute to any additional adverse human health effects. This approach to risk reflects scientific advances that have resulted in increasingly sensitive analytical methods, as well as more sophisticated risk assessment techniques. Residue analytical methods are now able to detect chemical substances in our food at parts per billion levels or less. Advances in risk assessment have enabled FDA to conclude that in some circumstances, some substances shown to be carcinogens in high-dose animal studies represent no risk to human health when present in minute quantities in the food supply under specified conditions of use. This was also the conclusion reached by the National Academy of Sciences in its report, Regulating Pesticides in Foods: The Delaney Paradox.

A negligible risk approach that takes these scientific advances into account is quite familiar to us, since as you know, we have used or proposed it ourselves in a number of cases. We support the use of this concept as the basis for the establishment of pesticide tolerances in this legislation. We also strongly urge that this concept be applied to food and color additives. To leave these substances out could create confusion about food safety.

How Specific Should Negligible Risk Be?

We believe, however, that there are many drawbacks to the specific language contained in S. 722. First, FDA is concerned about the bill's use of specific numbers to define negligible risk. Such specificity is inappropriate for two reasons. First, as we learned with Delaney, science will progress. A concrete number in the statute will not. Consequently, even though we have made and continue to make regulatory decisions on the basis of risk assessments of one in a million under our "sensitivity of method" regulations, we urge that legislation avoid codifying a specific number--even one in a million--in the bill to define negligible risk. Second, we have reservations about codifying specific risk assessment methodology. Scientists use diverse assumptions and endpoints to estimate risk in a given situation. These differences in assumptions will affect not only the calculation and ultimate numerical representation of that risk, but also how scientists interpret that number. In short, we believe that risk assessments, and the assumptions used in each assessment, must be based on the particular facts in each case.

Other Considerations

FDA is also concerned that unlike last year's bill, S. 722 fails to allow the substitution of one pesticide for another in special situations when neither pesticide meets the negligible risk standard, but the benefits from the substitution outweigh the risks in the status quo. If a newer pesticide with greater than negligible risk is a safer alternative to a currently used pesticide of greater risk, substitution should be allowed.

The bill also requires that, after six years, the cumulative effects of all pesticides be considered in determining "negligible risk" for a particular agricultural commodity. This provision is unclear. If it is the intent of the bill to require calculation of a pesticide's interactions with other chemicals or the potential for synergistic or antagonistic effects, FDA believes that the expertise and technology necessary to predict the cumulative risk of combinations of individual chemicals do not currently exist. We doubt that this requirement could be met.

METHODS FOR RESIDUE MEASUREMENT - EPA/FDA CONSULTATION

The bill would prohibit EPA from establishing a tolerance or maintaining an existing one until a practical method for detecting and measuring the residues had first been developed in consultation with FDA. "Practical" is defined in the bill as the "best available" method that can be performed "routine[ly]" as part of surveillance and compliance sampling with available personnel, equipment, and other resources.

This provision reinforces an existing informal relationship. Formal consultation between FDA and EPA is essential to assure that a suitable analytical method to detect and measure a pesticide residue is available before a tolerance is established. Indeed, FDA works actively with EPA to evaluate methods of residue analysis suitable for enforcement. For example, we have ongoing consultation regarding the FDA's Pesticide Analytical Manual, Volume II, which is edited and funded by FDA. The Manual is used world-wide as the authoritative reference on pesticide residue methods and is cited in the Code of Federal Regulations for enforcement purposes. Liaison between FDA and EPA has been further strengthened through the formation of an Interagency Pesticide Residue Methods Committee, formed to improve and maintain the suitability and performance of analytical methods for pesticide residues.

We support this concept of formal consultation between the agencies to assure that a suitable analytical method exists before a pesticide is approved. Currently, FDA conducts research to develop methods for pesticides already in use. FDA is concerned, however, that the bill may limit FDA's flexibility in selecting an appropriate method to detect a pesticide residue. Before adopting a particular method for use in its monitoring programs, FDA scientists consider, among other things, whether the method can measure a residue at or below the specified tolerance, what the complexity, reliability, and sensitivity of that method may be, how much time would be required to perform an analysis, and whether it is a multi- or single-residue method. If the intent of this legislation is to require FDA to test every new method that is developed to determine whether it is better than one currently used, and thus, the "best available," then scarce Agency resources could be diverted from surveillance and enforcement activities. Once EPA and FDA agree on the adequacy of a test that is sensitive to a level sufficiently below the tolerance, FDA should be able to rely on use of that method.

FDA is also concerned that the requirement for "routine" testing might be construed to require FDA to run each method on all samples collected or restrict our selection of the most appropriate analytical method in a particular situation.

INERT INGREDIENTS

The bill would expand the definition of "pesticide chemical" to include inert ingredients of pesticides. It would require tolerances for these substances as well as for the parent pesticide.

FDA agrees that inert ingredients used with pesticides may have potential adverse health effects. In 1987, EPA outlined its policy for regulating inert ingredients, and identified over 1200 inerts used with pesticides. EPA categorized these inert ingredients according to the potential hazards they might present, as well as those where no information about hazard was available. EPA also indicated its plans to set tolerances for some of these chemicals.

We recommend EPA complete its evaluation of these ingredients and set tolerances for the inerts that pose hazards, rather than to require a tolerance to be set for each and every inert, as required by the bill, regardless of its potential for toxic effects. FDA is concerned that if this provision as currently drafted were enacted into law, it would require enormous increases in pesticide program resources to provide for monitoring these chemical residues.

USER FEES

The bill authorizes EPA to impose and collect fees related to registering and establishing tolerances for pesticides. FDA believes this authorization should be expanded to cover the costs of the additional activities required by the FDA under this bill. S. 722 would require FDA to approve analytical methods for pesticide residues in consultation with EPA, and to sample and analyze foods for inert ingredients of pesticides, consistent with the bill's broader definition of "pesticide chemical." FDA also expects that the bill will require additional monitoring, sampling, and analysis to provide EPA with data for estimating dietary exposure to chemical residues identified in the bill. FDA recommends that consideration be given to authorizing user fees to cover FDA's costs for monitoring and enforcing tolerances and determining the suitability of analytical methods.

CONCLUSION

In sum, we believe that the provisions of the bill concerning negligible risk represent a significant advance in public policy and an important first step towards updating the law to reflect improvements in scientific knowledge and methodologies. Rational food safety law reform is warranted in light of what we now know about chronic exposure to chemicals and the progress science has made since the Delaney clauses were first enacted. FDA further suggests that consideration be given to revising the Delaney clauses that apply to food additives and to color additives as well. Federal programs designed to reduce cancer risks should be consistent, whether the potential for risk stems from pesticides, food additives, or color additives.

While we have serious concerns about the bill as currently drafted, we are ready and willing to work with the Committee staff to discuss ways in which our concerns might be resolved.

Thank you, Mr. Chairman. If you or members of the Committee have any questions, I will be pleased to answer them.

Risk Analysis, Vol. 6, No. 2, 1986

FDA Color Report

Final Report of the Color Additive Scientific Review Panel[1]

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The Color Additives Scientific Review Panel considered whether there was information sufficient to perform a carcinogenic risk assessment on the colors D&C Red No. 19 (R-19), D&C Red No. 37 (R-37), D&C Orange No. 17 (O-17), D&C Red No. 9 (R-9), D&C Red No. 8 (R-8) and FD&C Red No. 3 (R-3) and to evaluate the assessments sent to FDA as part of the petitions for use of the colors for drug and external uses by the Cosmetic, Toiletry and Fragrance Association (CTFA). There is a lack of human data concerning the colors for making a human health assessment, so the assessments are based upon the extrapolation of animal data. The risk assessments are determined for exposure to single chemicals. Excluded from consideration are possible effects from exposure to multiple chemicals, such as co-carcinogenesis, promotion, synergism, antagonism, etc. In the light of recent efforts in establishing a consensus in risk assessment, the Panel has determined that the CTFA assessments for R-10, O-17, and R-9 are consistent with present acceptable usages, although it questions some of the assumptions used in the assessments. The Panel identified a number of general assumptions made, and discusses their validity, their impact on total uncertainty, and the potential options to address the gaps in understanding that necessitate the assumption. The Panel also derived revised risk estimates using more "reasonable" assumptions than "worst-case" situations, for 90th percentile and average exposure. For those assumptions that are easily quantifiable, the Panel's estimates are less than an order of magnitude lower than the CTFA risk estimates, indicating that the underestimates and overestimates of the CTFA risk estimates tend to balance each other. The impact of most of the assumptions is not quantifiable. The assessment for R-3 is complicated by the fact that there is no good skin

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[1] Because the original audience for this document was fairly broad it contained a good deal of background explanatory material and a number of summaries. For presentation here, the document has been shortened by removal of this material.

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penetrance study for this color. It was assumed that the penetrance is similar to that of another water-soluble xanthene color, R-19. It is expected that the absorption of the color is not likely to exceed that of the smaller molecule, R-19. Therefore, the risk estimates are similar to the CTFA estimates, but with different reasoning. The estimates for R-8 and R-37 are different from the others in that there is a lack of any exposure or toxicological information on these colors. The toxicological properties were considered to be similar to the chemically related colors R-9 and R-19, respectively. The risk calculated for these dyes is actually a unit risk (i.e., a risk based on particular unit exposure). The unit exposure used is the exposure estimated from the chemically related color, which, from the production values for the dyes, is likely to have much higher usage. Exposure to all of these colors from external and drug uses is quite low, especially as a result of exposure through skin. Therefore, the risk estimates are low. It is cautioned that usage information is based on a recent survey, and changes in usage will alter the risk estimate.

KEY WORDS: Risk assessment; color additives; FD&C Red No. 3; D&C Red No. 8; D&C Red No. 9; D&C Red No. 19; D&C Red No. 37; D&C Orange No. 17; assumptions.

1. INTRODUCTION

The 1960 Color Additive Amendments to the Federal Food, Drug, and Cosmetic Act allowed temporary "listing" (i.e., permission to be marketed) of then-marketed color additives pending completion of studies to determine their safety.(1) The "provisionally listed" additives deemed safe were to be "permanently listed." Approximately 200 color additives were involved, of which 126 have been "permanently listed" and 63 eliminated. Ten additives remain on the "provisional list"; six are considered in this report: D&C Red No. 19 (R-19), D&C Red No. 37 (R-37), D&C Orange No. 17 (O-17), D&C Red No. 9 (R-9), D&C Red No. 8 (R-8), and FD&C Red No. 3 (R-3).

An important part of the safety determination of these colors, because of the available toxicological evidence, is estimation of their carcinogenic risk. Information supporting continued marketing of the additives has been submitted to the Food and Drug Administration (FDA) by the Cosmetic, Toiletry and Fragrance Association (CTFA), that purports to show minimal risk from drug and cosmetic uses. These submissions include risk assessments for R-19,(2) O-17,(3) R-9,(4) and R-3(5) and an analysis of certain objections to these risk assessments.(6) The CTFA analyses have been challenged on a number of bases, including scientific ones, with the suggestion that valid risk assessments cannot be performed on these colors.(7)

In order to insure the use of the best science in FDA determinations, and as part of a continuing process of peer review, the Commissioner of Food and Drugs charged a Panel consisting of knowledgeable scientists from a number of Federal agencies to evaluate: (1) the possibility of performing a scientifically valid carcinogenic risk assessment of the six colors for drug and cosmetic uses; and (2) whether the available information supports the risk analyses before the FDA. These deliberations were done against the background of recent reports which are developing a consensus on risk assessment.(8-10)

2. CTFA RISK ASSESSMENTS

2.1. Summary of CTFA Risk Assessments

In very brief summary, the submitted CTFA risk assessments contain:

1. Chemical identification of the six colors and their impurities.
2. *Hazard Identification* —Description of *in vitro*, short-term, and long-term animal assays including two-generation studies, used for both evidence for carcinogenicity and in deriving risk estimates. This was done for four colors (R-3, R-9, R-19, O-17), and assumed that the response of R-37 was similar to R-19, and R-8 similar to R-9 on an equal color basis.
3. *Exposure Assessment* —Including: a listing of color-containing generic cosmetic products with color concentration; estimates of the amount of product per application; asses-

ment of usage using two surveys; estimation of the color applied available for skin absorption; assessment of human skin penetrance using an *in vitro* model.

4. *Dose-Response Assessment* —Using positive cancer bioassays and a linearized multistage model.
5. *Risk Characterization* —Discussion of important assumptions such as:
   a. Animal cancer response can be extrapolated to humans using a metameter of mg/kg-day;
   b. Dose-response can be extrapolated from high doses used in the animal experiments to the low doses seen in humans;
   c. The colors absorbed through the skin would evoke the same response, qualitatively and quantitatively, as colors absorbed on an equal absorbed dose basis;
   d. The total absorbed dose per day equals the frequency of application times the concentration of color in the products times the amount of product per application times the color resorption rate.

It was also suggested that the uncertainties in the risk assessments were approached using conservative assumptions (i.e., assumptions that err on the safe side and were unlikely to underestimate risk).

2.2. Evaluation of CTFA Risk Assessments

The Panel basically agrees with the risk assessment methodology used by CTFA, but it questions some of the assumptions used in the analyses. Many assumptions are explicitly stated, others become apparent only after a careful consideration of CTFA's line of reasoning, or of the methodology used. A number of these assumptions are commonly made in conducting a risk assessment. Use of an assumption by CTFA does not necessarily imply that it considered the assumption valid. Indeed, many of the assumptions were made for the explicit purpose of deriving what the CTFA characterized as a "conservative risk estimate" by overestimating exposure, and were often followed by a discussion reflecting CTFA's awareness that the assumption was erroneous. The assumptions in the CTFA assessments are listed below, with the Panel's analysis, followed by revised estimates for the risk in each color-specific section.

Since, in certain cases, generating data rather than making assumptions may provide information which can reduce the number of necessary assumptions and their associated uncertainties, suitable and feasible studies are sometimes suggested.

3. GENERAL ASSUMPTIONS USED IN THE RISK ASSESSMENTS

3.1. General Assumptions Used in the Hazard Identifications

- *Assumption 1:* Any carcinogenic response in an animal test predicts a carcinogenic response in humans.

Validity: Unknown. It has been shown that all human carcinogens are also animal carcinogens in some assay. However, relatively few animal carcinogens have been shown to be carcinogenic in humans. This may reflect either lack of, or deficiencies in, design and implementation of epidemiologic studies. On the other hand, humans may be insensitive, or the animal model may not mirror the human response. For its deliberations, the Panel did not evaluate the weight of evidence for human carcinogenicity since it understood that it was FDA policy to consider an agent which is carcinogenic in some experimental paradigm, in any species, as a suspect human carcinogen. If the weight of evidence would have been evaluated, there is the possibility that one or more of the colors would not have fulfilled some accepted criteria (e.g., IARC criteria(11)) to be considered human carcinogens. In this framework, the Panel accepted the use of the above assumption.

- *Assumption 2:* The carcinogenic potential of a chemical is independent of route of administration and the medium used (i.e., if the colors are shown to be carcinogenic after oral exposure, it is assumed that skin application would induce cancer as well unless there is evidence to the contrary).

Validity: Testable by conducting chronic assays by skin application. Skin carcinogenesis tests have been uniformly negative for the colors of concern. However, as the amount of material expected to penetrate the skin in these tests was low compared to the amounts tested in the ingestion assays, the Panel accepted use of the assumption, attempting to adjust for differential exposure resulting from skin penetrance compared to oral exposure (see also assumption 2 in section 3.2 below).

- *Assumption 3:* An animal bioassay is more appropriate for hazard identification if the chemical is tested at or near the maximum tolerated dose (MTD). It is assumed that critical metabolic pathways are not overwhelmed and carcinogenic mechanisms are the same regardless of dose.

Validity: Unknown and, at the current state of the science, difficult to test. Generally, animals are placed on test when 6–8 weeks of age for a chronic bioassay. To increase assay sensitivity, multigeneration protocols are also employed; in such studies the animal is exposed at all stages of development, including organogenesis and rapid proliferation, presumably more sensitive stages of development. The use of this protocol requires an expanded definition of the MTD since a toxic dose and toxic effect for an embryo may be very different from that for an adult organism. Although this was not done, the Panel used this assumption.

3.2. General Assumptions Used in the Exposure Assessments

3.2.1. Nonproduct-Specific General Assumptions

Humans are exposed to the colors of concern by means of cosmetics, drugs for skin application, and products for personal hygiene. The Panel chose to derive two different estimates of exposure: (1) the 90th percentile exposure values (i.e., equal to a value that is more than or equal to that which is expected for 90% of the population affected, understanding that it was a long-standing FDA practice to use this value); and (2) an approximate "reasonable" estimate, based on the anticipated average or mean exposure.

- *Assumption 1:* Orally administered or ingested colors are absorbed equally well in test animals and man, regardless of the test concentration of the color and the vehicle used.

Validity: Unknown; it is testable, although rarely done in risk assessments.

Option: Conduct comparative absorption studies in test animals and man.

Impact: The quantitative impact of the assumption on the risk estimate is unknown, it may result in under- or overestimation of the risk. The Panel accepted use of the assumption.

- *Assumption 2:* In comparing routes of administration, the amount of color which penetrates the skin will be equally effective as the amount which penetrates the gastrointestinal tract in evoking a carcinogenic response.

Validity: Unknown and testable. There is good evidence that gastrointestinal microflora and skin can activate carcinogens by very different mechanisms (see also assumption 2 in section 3.1).

Option: Conduct studies which deliver similar systemic doses by various routes in appropriate animal model systems.

Impact: Depends upon carcinogenic mechanism and agent metabolism, which have not been characterized well. The Panel accepted use of the assumption.

- *Assumption 3:* Relative absorption in humans can be estimated under standardized experimental conditions using 2–5 days postmortem abdominal skin specimens.

Validity: Unlikely to be valid, testable. The assumption is based upon the implied claim that a postmortem skin specimen does not differ from live skin with regard to permeability, that skin preparation can be standardized, and that abdominal skin represents other areas of the body as well.

The skin penetration studies[12–15] use an *in vitro* skin test model consisting of a 1- or 2.5-cm^2 section of human skin mounted in a diffusion cell. The dermal surface of the skin was placed in isotonic saline at pH 7.4 and 37°C. The bathing solution (the receptor phase) was removed and sampled at regular intervals. For some colors, it was replaced by a Volpo-20 solution to increase color solubility. The colors were applied in various concentrations and vehicles (simulating, to some degree, the composition of commercial products), in volumes of 5, 10, or 25 μl, or as 25 mg talc. The radioactively labeled colors were left *in situ* for periods of 2–3 days, and the absorption of color through the skin into the receptor phase was measured with a scintillation spectrometer. The skin sections were obtained from the abdominal skin of deceased hospital patients within 24 h of their death, and used either immediately or refrigerated for no more than 20 h. Before mounting in the diffusion cells, the subcutaneous fat tissue and approximately 50% of the dermis was removed by shaving with a scalpel. In a number of cases, the epidermis was also tested (separately from the dermis), in order to investigate the effects of differential retention on tissue permeability.

A number of factors are important in estimating human percutaneous absorption, including the application of *in vitro* to *in vivo* results, site of application, and individual variation.(16) The percent dose absorbed of triclocarbon (sic, triclocarban) was significantly different in a static *in vitro* system compared to an *in vitro* continuous flow system.(16,17) Since the paradigm involved changing the bathing solution and altering vehicle to simulate the solubilizing effects of blood flow, the experimental system used was probably more similar to the continuous flow system than a static diffusion cell. Since the continuous flow system appears to be a fairly good model for *in vivo* human skin for triclocarban, and the *in vitro* models overestimated the *in vivo* penetrance of another chemical (paraquat), the Panel determined that although there appears to be significant variation with different chemicals the *in vitro* model was not likely to significantly underestimate skin penetrance.

Options: Conduct rigidly standardized *in vivo* and *in vitro* studies using live skin at various sites (in particular facial and scalp).

Impact: There are insufficient data available to assess the quantitative impact of using postmortem skin sections, but the model is very likely to overestimate the true absorption rate. Since postmortem skin disintegrates with time, it is likely that the skin's integrity as a barrier will be affected. The longer the time since death, the more permeable the skin becomes. Another aspect of the skin model is that artificial canals between the skin surface and the receptor phase have been created by cutting through the sweat and hair ducts. The effect of this artifact has not yet been quantified but will result in raising the observed absorption rate. On the question of differential absorption as a function of site of application, for a few chemicals tested such as parathion or malathion, the urinary excretion of labeled material as percent of applied dose from jaw or forehead is less than three times higher than in glabrous abdominal skin.(18) Scrotum and vulval skin absorb more than the forehead.(16) Other experiments looking at the absorption of hair dyes under practical conditions of application indicate that an important factor is the surface area of the hair in the region, and it is suggested that the 75–100 times larger surface area of hair on the scalp is the main factor in the relatively low scalp penetration of hair dyes (0.02%) that penetrate 100 times more in the ventral aspect of the forearm.(19) From these data, it is likely that penetration rates for the colors under consideration vary in different areas of skin. In order to model absorption through all skin areas, especially for products used all over the body (e.g., bath products, soaps, etc.), the Panel used the data from the tests conducted on abdominal skin and multiplied by an overall average absorption value of three. This is probably a conservative estimate.

- *Assumption 4:* For each color, the skin absorption rate equals the steady-state rate, unless this is not reached after 3 days, in which case twice the maximum rate at that time is used to approximate the absorption rate.

Validity: Seems reasonable for the steady state, but not for the maximum rate and is testable. Much depends on how well the *in vitro* skin test reflects reality. It is hard to understand a continuous rising trend in the absorption rate through healthy and live skin, but it is easy to understand for a skin section 5 or more days postmortem. Since it may be expected that with increasing time postmortem, a degenerating skin will become more penetrable to the colors, the absence of a steady state may suggest the presence of an artifact.

Option: Repeat the skin tests with live skin for extended periods of time.

Impact: Since the absence of a steady state after 3 days may reflect a postmortem skin artifact, the assumption that twice the maximum rate represents the true absorption rate probably results in overestimating the exposure. The Panel considered this assumption, when relevant, in the color-specific sections.

- *Assumption 5:* The CTFA-sponsored usage frequency surveys are representative of the usage pattern in the population of users of cosmetics and drugs for external use.

Validity: Probably incorrect and testable. CTFA conducted two surveys on the use of cosmetics and hygiene products. The usage surveys included a one-week prospective survey of 47 female CTFA employees and their families, and a retrospective survey among 1129 customers of a retail chain run by a major cosmetics producer. Data were available to the Panel for R-3, R-9, R-19, and O-17.(2-5) The prospective study included CTFA female personnel and their families, while the retrospective study involved clients of a cosmetics retail chain only. It is not clear whether male clients were also included. It is very likely, in both surveys, that males have been underrepresented, while there is an overrepresentation of frequent users. Further, interviewees of the retrospective survey are likely to be limited to products of one manufacturer only and, thus, have less variation in products (and, consequently, in dose levels) to choose from.

Options: Conduct surveys among the general population and provide data by age category (e.g., infants, older children, adults, elderly) and gender.

Impact: In general, the prospective study appears to be less biased than the retrospective study. It also yielded an approximately 15% lower usage frequency than did the retrospective study. It is unknown to what extent exposure is overestimated by the nonrepresentativeness of both surveys with regard to the population of product users. In the absence of more appropriate data, the Panel accepted use of the CTFA assumption, appreciating that it overestimates the risk. Since the prospective study seems to be less biased, when possible, exposure was determined with data from this survey.

- *Assumption 6:* For each color, the exposure is for a lifetime.

Validity: Obviously invalid and testable.

Options: Either: (a) make a more appropriate estimate based on practical considerations, and consider males separate from females; or (b) provide realistic estimates for each product based on surveys among the general population (as opposed to the clientele of these products); or (c) provide a realistic estimate for all products combined, based on surveys among the general population.

Impact: If exposure started, on the average at age 10, exposure would be for 6/7 of an average lifetime. The Panel used 6/7 of the CTFA exposure estimate, also accepting the assumption that the relationship between exposure and risk is independent of the age at exposure.

- *Assumption 7:* People use only products that contain the carcinogenic colors of concern.

Validity: Obviously invalid and testable.

Option: Conduct a survey on actual use of colored and uncolored products in the general population. It is appreciated, however, that patterns of use can change with time.

Impact: The available data are not sufficient for an accurate impact assessment. In order to reflect the wide variety of products available and the production figures of these colors compared to all the colors, the Panel used an arbitrary factor of one half to "correct" the assumption. However, more accurate data will probably revise this figure downward. This 0.5 factor is not likely to underestimate the risk and is assumed to be more reasonable than assuming 100% use of products containing carcinogenic colors.

- *Assumption 8:* People use only products with the highest concentration of the color.

Validity: Invalid and testable.

Option: Conduct a market survey on the concentration of products.

Impact: The survey of products containing R-19 cited in the risk assessment(2) indicates that the average concentration used in a product is less than 1/4 of the maximum concentration permitted in commercial products. The Panel used this factor for R-19 and, given the lack of any other information, also assumed that this is true for the other colors of concern.

- *Assumption 9:* The daily absorbed amount of color per product used equals:

$$a \times b \times c$$

where a = the amount of color in the product per application; b = the frequency of application (following the usage survey); and c = the percent absorbed per day of applied amount.

Validity: Unknown, it can be challenged.

Option: Conduct *in vivo* and *in vitro* (with live skin) studies and measure the amount available for absorption (rather than the amount applied), the amount applied per cm^2, the surface covered by the product, for varying frequencies of application per day with soluble and insoluble colors.

Impact: Since the value of c depends on many variables, such as the equilibrium between penetration rate and tissue retention, the amount of color lost by wiping or wearing off (i.e., the difference between the amount applied and the amount available for absorption), the thickness of the applied layer of product, the diffusion rate of color in this layer, etc., there may be either an under- or overestimation of exposure, by using the above approximation. Typically, cosmetics are regularly removed by cleaning or wearing off. The amount applied to skin in the diffusion cell did not account for the loss of material occurring *in vivo* (e.g., by wiping off excessively applied cosmetics, wearing off or rubbing off, and cleaning). Estimates of this loss of material can be made but are necessarily crude in the absence of adequate test data. If the cosmetic is not immediately reapplied, the absorption will probably drop because the steady-state absorption rate, reached *in vitro* after three days, will probably not be reached (this consideration is especially germane to the more insoluble colors which reach the steady-state absorption rate much more slowly than the others). Thus, the use of the steady-state rate in the above equation would overestimate exposure. However, a model which is based on one application in 2–3 days, when the real-life situation includes more frequent applications, will underestimate exposure because frequent application will cause the average concentration of the thin color layer directly in contact with the skin to have a higher average concentration (it doesn't become as depleted and as dependent on diffusion from the more color-rich layers above to replenish it in a short time as opposed to 2–3 days). This is, again, especially significant for the insoluble colors since the diffusion rate (and replenishment) will be slow. Since no information is available to support and/or quantify the above considerations, the Panel accepted use of the CTFA assumption.

- *Assumption 10:* For each color the total exposure is the sum of exposures to all products containing the color of concern.

Validity: A reasonable and testable assumption.

Option: Test mixtures rather than single colors.

Impact: Although unlikely, it is possible that there is interaction between the colors or that there is some change in skin penetration as a function of the number of colors being present. Interaction with the various kinds of vehicles may lead to either under- or overestimation. However, the overall impact is not likely to be substantial. The Panel used the assumption.

- *Assumption 11:* The amount of consumer product per application is 5–10 mg/cm^2.

Validity: Unknown, but testable assumption. In the CTFA risk assessments, values have been listed without reference and lacking information about distribution.

Option: Establish a database on the amounts of color used per application and the skin area exposed, through a general survey of the population.

Impact: Since there is no information, this assumption cannot be assessed. It may over- or underestimate exposure. The Panel accepted use of the CTFA assumption.

- *Assumption 12:* Differences in the vehicles used in the skin absorption studies are not likely to result in changes in the absorption of more than 10–30%.

Validity: Unknown but testable. There may be little similarity between the vehicle used in the absorption studies and the actual test product [e.g., nail polish uses vehicles which ensure fast evaporation to form a tough water- (and serum-) insoluble film].

Option: Expand the skin studies to include vehicles more similar to those used in consumer products.

Impact: Without data, no accurate estimate can be made of the effect of the test vehicle. There are no data to support the estimate of a 10–30% variation, nor is there any information on the direction of the difference. In the absence of data, the Panel used the CTFA assumption.

- *Assumption 13:* In an appropriate vehicle, there is no difference between a color in a formulation used as a primary color or in a lake form (frequently used in cosmetics, a lake is the salt of the color extended on a substratum of alumina, clay, titanium dioxide, etc.).

Validity: Unknown, but testable. Making a lake presumably makes the color more insoluble, thereby decreasing the unbound concentration which governs the rate of absorption. This prevents color leaching, is useful in cosmetic applications and may change skin penetrance.

Option: Conduct skin absorption studies using both lakes and primary colors.

Impact: There are no data available for assessing the impact. Since the lakes are made to restrict the water solubility of the color, their use would probably result in less absorption through the skin. In the absence of data, the Panel accepted use of the assumption.

- *Assumption 14:* That the major constituent of the color is the one of primary toxicological concern and can be modeled by the skin absorption test.

Validity: Reasonable and testable.

Option: Repeat skin absorption studies and evaluate the impurities for differential absorption and carcinogenic "potency."

Impact: No data available for an accurate impact assessment. The colors are not single chemical entities despite their categorization with simple chemical names (e.g., R-19 is frequently termed Rhodamine B). FDA certification requirements are generally not rigorous. They do not fully characterize the purity of the color (as percent of color additive) or the amounts and variety of impurities that may be present. For example, methods to determine "% color," often confused with "% purity," are based on the reduction of the color with titanium trichloride or the determination of total color, by weight, using spectrophotometry. Thus, subsidiary colors (colored analogs which are closely related chemically) would usually be included with the "pure color" as "% color" by these nonspecific methods. The certification requirements also specify the levels of some starting materials, volatiles, organic solvent-extractable compounds, subsidiary colors, salts, and inorganic contaminants. The methods used in certification are often neither state-of-the-art nor chemically definitive. In addition to impurities allowed by the certification process, FDA,(20-26) Environ,(6) and others(27-32) have speculated on the large variety of *possible* impurities that may be present as a result of side reactions during synthesis, products from impure starting materials, and in some cases color-derived degradation products.

The Panel judged that the major issue concerning impurities was not those that were possible, but those that were actually quantitated in FDA certified lots, particularly in those lots used in the carcinogenicity bioassays. The impact of these impurities on the risk assessments depends not only on their concentrations, but also on their carcinogenic "potency" and, for external uses, skin penetrance relative to the major color additive. Reasonably definitive analyses have been reported for these certified lots by more rigorous methodology than that required by the certification requirements. In terms of impurities actually present, the contaminants of major concern are the subsidiary colors and the residual starting materials.

For the subsidiary colors, even if they were carcinogenic and present at 5% by weight (the maximum reported amount), close similarity in chemical structure to the main color would probably preclude large differences in skin penetration rates and/or potency. Thus, the risk assessment remains basically unaltered.

For the residual starting materials, the highest concentrations found have not exceeded 1% by weight, with those chemicals related to known mutagens or carcinogens (such as the aromatic amines) not exceeding 0.5% by weight. In the special case where the color additive may be metabolized to a split product (such as an aromatic amine, and this material is present as a starting material impurity), the bioavailable aromatic amine in humans would be the sum of the dermally absorbed impurity and the metabolic product of the dermally absorbed color additive. Estimating the potency and penetrance of the actual impurities, the Environ Report(6) and the other available data indicate that it is highly unlikely that these impurities could be totally responsible for the reported carcinogenic effect or that the contribution from the starting material would be significant compared to that available from the metabolism of the intact color additive.

More quantitatively, the residual starting materials are unlikely to be more than five times as "potent" (i.e., equivalent in effect to five times the amount of major component), and 10 times as capable of penetrating the skin, as the major color component. If this "worst case" is so, their maximal effect can be estimated, in terms of exposure, as follows:

It is useful to define a μg toxic-color-equivalent (μ-tce) as the color-equivalent (in μg) × "potency" × the absorbed %. In these terms, if the color is pure major component (and subsidiary colors) (with "potency" 1) for a gut absorption of 50%, one mg color equals 500 μ-tce. In the skin, with absorption of 1%, 1 mg equals 10 μ-tce. Assuming pure color, the "dose" from skin exposure of 1 mg is therefore expected to be 10/500 of the same amount in the ingestion studies. However, maximally, 1 mg of commercial color used in the ingestion studies consists of 995 μg of major (and subsidiary color) components of "potency" 1, and, 5 μg (0.05%) of starting material with "potency" 5. This equals 497.5 μ-tce (from the major component) + 12.5 μ-tce (from the starting materials), or 510 μ-tce. Similarly, in skin, 1 mg of maximally contaminated color, assuming 1% penetrance of the major component (and subsidiary colors) and, again maximally, skin penetrance of 10% for the more "potent" contaminants results in 9.95 μ-tce (from the major components) and 5 × 5 × 0.10 = 2.5 μ-tce (from the starting residuals) or a total of 12.4 μ-tce. Therefore, the "dose" expected as a result of skin exposure from 1 mg of color .with maximal impurity contamination could be equivalent to as much as 12.4/510 of that amount in the ingestion studies [i.e., a factor of (12.4/510 + 10/500) or 1.22 times the exposure].

Thus, to account for significant impurities (starting materials and subsidiary colors), a factor of 1.22 times the CTFA exposure estimate was used.

3.2.2. Product-Specific Assumptions

- *Assumption 1:* For hair cosmetics, 2% of the applied color reaches the skin (i.e., the ratio of skin area to hair area is assumed to be 1:50).

Validity: The total surface of hair is 75–100 times the surface of the scalp. Using 1:50 seems conservative if the total hair surface is indeed 75–100 times the skin surface, a figure which may be an underestimation for females.

Option: Compile data on hair length, diameter, and density.

Impact: No data available for an accurate estimation. If the estimate is too low, the risk estimate is proportionally too high. Since the skin/hair surface ratio of 1:75, or 1.33% reaching the skin, may already be high, further raising it to 1:50 appears to be an unnecessary application of a safety factor ranging from 2/1.33 = 1.5 to (for a ratio of 1:100) 2/1 = 2.0. The Panel used what it considered to be a more appropriate figure, 1.75%, or approximately 1:60.

- *Assumption 2:* For nail products, 1% of the applied color reaches the skin or the cuticle.

Validity: Reasonable and testable, but it still does not account for vehicle volatility.

Option: Conduct a test of nail products under realistic conditions.

Impact: Since the solvents in nail polish are highly volatile and nail polish is intended to dry up to an insoluble film almost immediately after application, the penetration rate of colors in such products is virtually zero. Therefore, it is very unlikely under this condition that a measurable color absorption would occur in the very brief period of application. Theoretically, absorption of color from nail creams and lotions is possible. But the test model did not evaluate nails as the area of application. Given the low frequency use of this product(2–5) and, in view of the above discussion, assuming a zero absorption of colors from nail products is, in practice, not an underestimation of the risk. The Panel assumed zero absorption from nail products.

- *Assumption 3:* For bathwater products, 2% of the applied color reaches the skin. It is assumed that a layer of 1 mm of water, equaling 1.8 l of water, would cover the body to form the source from which color can be absorbed; this is 1.8% of an assumed 100 liters of bathwater.

Validity: Reasonable and probably testable.

Option: Conduct an *in vivo* study of animals immersed in a color solution.

Impact: Unknown due to lack of data, but not likely to be significant. The Panel accepted the assumption used by CTFA.

- *Assumption 4:* Products used for a short period only (wash-off products) have an absorption of 50% of that of products in continuous use, regardless of how short the actual exposure was.

Validity: Seems incorrect and is testable.

Option: Repeat skin test focused on amount of color retained in the skin during various short periods of time.

Impact: The skin test data(12–15) suggest that the absorption for wash-off products is far less than 50% of that for products with continuous use. Hence, exposure is considerably overestimated. Since an absorption rate of 25% of the rate for products used continuously seems more realistic, the Panel used a correction factor of 0.5 for the CTFA exposure estimation. More information is required for a more accurate quantification of the assumption.

- *Assumption-5:* For products other than wash-off products it is assumed that the amount applied equals the amount available for absorption.

Validity: Incorrect and testable. It is likely that in most applications of cosmetics they are applied in excess and they wear or are rubbed off. Therefore, the amount left for absorption is less than the amount applied. The overestimate of exposure is related to the amount removed (i.e., not available for absorption).

Option: Conduct studies focused on measuring the proportion of applied product that is either removed by wiping off or by contact with materials other than skin (e.g., clothes).

Impact: The amount of color available for absorption is hard to quantitate. It seems reasonable, however, to assume 50% loss for products other than wash-off products; therefore, the Panel used a factor of 1/2. This correction factor should not be applied to products in a water-alcohol vehicle.

3.3. General Assumptions Used in the Dose-Response Assessments

- *Assumption 1:* In long-term rodent-feeding studies, there is 100% absorption of the colors.

Validity: Unknown and is testable. The colored feces seen in some studies suggest that some color was not absorbed. However, because of processes such as biliary excretion, elimination of the compound in the feces does not necessarily indicate lack of absorption. Some of the benzidine azo dyes, which also resulted in colored feces, demonstrated low absorption when given by the oral route. A likely absorption range is 25–75%.

Option: Conduct absorption studies for oral administration.

Impact: Unknown, and may lead to an underestimate of risk for externally used products. If only 50% of the carcinogen is absorbed from the feed, then tumors are produced by 1/2 of the administered dose. Hence, the CTFA risks for colors absorbed through the skin should be multiplied by 2, a factor the Panel used. No correction is needed for internal exposure from swallowed lip products, if the proportion absorbed by the oral route is similar in humans and rodents.

- *Assumption 2:* If a color is carcinogenic in humans, the risk of cancer for a lifetime exposure in humans is equal to the risk for a lifetime (approximately two years) exposure in rodents for equal daily doses on a body weight basis (mg/kg body weight-day).

Validity: Probably not true. Hoel *et al.*(33) suggested the use of mg/m^2 body surface area-day on the basis of the acute toxicity of anticancer drugs in humans.(34) Crump *et al.*,(35) using a data base derived from the NTP bioassays for over 200 chemicals, concluded that the dosage measurement giving the closest correlation between species was mg/kg body weight-day. However, use of relations such as these has led to concern. It has been noted that

> It does not appear safe to generalize concerning rates of unknown metabolic reactions. Many exceptions could be found to the apparent tendency of intrinsic rate to decrease with increasing body size: Quite different qualitative pathways may dominate in different species and toxicity may sometimes correlate with the concentration of an active intermediate that represents only a minor elimination pathway.(36)

It should be appreciated that studies on the distribution and metabolism of the principal components of the colors have been performed only for R-3 and R-9. Even these studies are not sufficiently extensive to decrease markedly the uncertainties in making the risk assessment. To achieve accurate estimates of risk, one requires knowledge of the metabolites and the mechanisms by which a carcinogen causes an increase in malignant tumors. Many interrelated factors will govern the incidence of carcinogenesis in a given study. Among these are species, strain, and individual differences in the relative distribution of enzymes that govern the formation of adducts in different tissues. Dose-dependent kinetics may occur, but the effects at different doses will be unpredictable. Environmental factors will also affect the fraction of the dose of the carcinogen that is converted to relevant metabolites. Oncology has not progressed to the understanding of all these factors even for the animals used in bioassays.(37) Even if these parameters were known for the bioassay, however, the probable influence of different environmental and genetic factors, and the heterogeneity in the distribution of these factors in the human population, should be appreciated.

There is no direct evidence to assess the relative carcinogenic potency of these colors between humans and rodents. However, for 15 carcinogenic agents, after defining "potency," relative "potencies" between humans and the most sensitive rodent data were generally within a factor of 20, either high or low, when dose was measured in terms of mg/kg body weight.(38) To generalize, for an individual chemical, the risk estimate calculated could be low or high by a factor of 100. Quantitatively, extrapolation on a surface area basis would multiply the CTFA risk estimates by approximately 7 for those based on rats and 12 for mice.

Option: Would require epidemiological data. Since anticipated cancer risks are small, an extremely large study would be required. Exposure would be difficult to measure and is not practical. Alternatively, pharmacokinetic analyses in combination with knowledge of the carcinogenic metabolites may be adequate to define a good metameter.

Impact: Unknown, could be substantial in either direction. The Panel used this assumption.

- *Assumption 3:* For extrapolation, a woman is considered to have a lifetime average body weight of 53 kg.

Validity: Probably valid for the general female population, unknown for the population of cosmetic users.

Option: Conduct a survey of weights among the product users.

Impact: A value of 60 kg as a lifetime average weight of the general population (including males) is commonly used by the FDA. Since the products are likely to be used predominantly by females, with males unlikely to be exposed to products having significant color concentrations (aftershave lotion, bath soap, etc., have very low color concentrations), it seems reasonable to accept 53 kg for the risk calculation. The Panel accepted use of the CTFA assumption.

- *Assumption 4:* The linearized multistage model provides an upper bound on low dose risk estimates in the convex portion of the dose-response curve.

Validity: Probably provides an upper bound on low dose risk estimates for the rodent species.(39) The appropriate model to choose for "best" estimates is unknown. Various models may fit the experimental data equally well, but may differ considerably at the lower doses. Even if the multistage model were appropriate, whether or not a linear term is included makes a considerable difference at the lower doses. If a linear term is present, the "best estimate" may be within a factor of two of the upper-bound estimate. If a linear term is not present, however, the "best" estimate may be several orders of magnitude below the upper-bound estimate. Thus, even restricting estimation to the multistage model cannot establish a "best" estimate because the high dose experimental data cannot establish the presence or absence of low-dose linearity. Therefore, "best" estimates should not be attempted as was done by CTFA even for the rodent species. The use of a model incorporating low-dose linearity is consistent with a recent suggestion by the OSTP carcinogen document.(9)

Option: Other linearized models could be used, but they are not likely to vary much from the linearized multistage model estimates.

Impact: If these colors act to add to carcinogenic processes already existing in humans, then low-dose linearity is expected. The choice of the model then offers no additional safety assurance and does not impact on the risk estimates. If the colors act by independent processes to produce cancer and low-dose linearity does not result, the upper-bound estimates may be higher than actual risk by several orders of magnitude. The Panel used this assumption.

- *Assumption 5:* The most sensitive animal tumor data (species-strain-sex-tissue or organ site) are the most appropriate indicator for human sensitivity and are generally used to estimate risk.

Validity: No direct evidence that this would or would not be a reasonable representation of very sensitive human subpopulations.

Impact: Unknown, could be substantial. The best animal model to predict cancer incidence in the "most sensitive" human subpopulations is seldom known and would probably vary with the carcinogen being considered. The Panel accepted use of this assumption, in accord with a recent suggestion.(9)

3.4. Risk Characterization

When the assumptions used in the CTFA risk assessments have been accepted by the Panel, it is frequently because there seem to be no alternatives with higher degree of validity for the uncertainties involved, and because some are consistent with what the Panel understands is FDA policy. The risk estimates given by the Panel are based on reasonable estimates of exposure, whenever the Panel believed that it was possible to make such an estimate. In situations in which available data would allow for a choice between "degrees of reasonable estimate," the Panel consistently selected the estimate associated with the higher risk, following prudent public-health policy.

For example, the use of an upper 95% confidence limit for the linearized multistage model utilized in the low-dose extrapolation probably leads to an overestimate of risk for rodents. If we also assume equal susceptibility for rodents and humans, and using the most tumor-sensitive site and species in conjunction with conservative estimates of exposure, the estimates presented are likely to lead to an overestimate of risks for humans.

3.5. Conclusion on the Total Impact of Assumptions on the Risk Estimate

In the following sections, the product- and color-specific assumptions are applied to the usage data contained in the CTFA risk assessments to derive the Panel exposure values (e.g., if absorption through the use of nail polish for a color was assumed to contribute 0.0002 μg/day to the total exposure, the use of the correction factor of zero results in this amount becoming zero). The Panel used these assumptions with survey estimates of 90th percentile exposure (the Risk/90 values) and average and "reasonable" estimates of exposure (Risk/Rea) to derive the revised risk estimates.

For the general assumptions above which are approximately quantifiable, for skin exposure, the correction factor accounts for:

i. General Exposure Assumption 3 (section 3.2.1.): 3

ii. General Exposure Assumption 6 (section 3.2.1.): 6/7

iii. General Exposure Assumption 7 (section 3.2.1.): 0.5

iv. General Exposure Assumption 8 (section 3.2.1.): 0.25

v. General Exposure Assumption 14 (section 3.2.1.): 1.22

vi. General Dose-Response Assumption 1 (section 3.3.): 2

$$(3\times 6/7\times 0.5\times 0.25\times 1.22\times 2) = 0.8\times \text{CTFA estimate}$$

For incidental ingestion of lip products, parameters relevant only to skin exposure or not relevant to lipstick products drop out (all except *ii*):

$$(6/7) = 6/7 \times \text{CTFA estimate}$$

At low dose levels, the estimated cancer risk, as computed with the linearized multistage risk model, is directly proportional to the dose levels.(9) Therefore, appropriate risk estimates, based on the adjusted exposure estimates (i.e., modified by the product and color-specific assumptions) are multiplied by the above correction factors to derive the Panel risk estimates.

The Panel recognizes that the correction factor of 0.8 for skin absorption is inconsequential compared to the uncertainties in the assumptions that are difficult to quantify. Less than half of the 24 identified assumptions are even approximately quantifiable, some only with fairly arbitrary factors. The correction factor for skin absorption does *not* mean that the risk estimate is precise within 20% of the actual human risk. What it does mean is that, for the various quantifiable assumptions, underestimates and overestimates of risk in the CTFA analyses essentially cancel out.

The assumptions, and the risk assessments that derive from them, are directed at estimating the effects from exposure to a single chemical only. They do not include possible effects of exposure to multiple chemicals such as co-carcinogenesis, promotion, synergism, or antagonism. Finally, when absorbed dose is cited to three or more significant figures, the use of this many figures does not imply precision; it is merely a mathematical tool to avoid cumulative rounding errors.

4. D&C RED NO. 19 (R-19)

4.1. Chemistry

D&C Red No. 19 (CI 45170) (R-19) (CAS 81-88-9) is the water-soluble xanthene dye 9-(2-carboxyphenyl)-3,6-bis(diethylamino)xanthylium chloride (FDA also terms it the 3-ethochloride of 9-o-carboxyphenyl-6-diethylamino-3-ethylimido-3-isoxanthene). Its common name is Rhodamine B and its structure is shown in Fig. 1.(20,40)

R-19 is synthesized from the condensation of phthalic anhydride and 3-diethylaminophenol to produce a colorless lactone intermediate, which is saponified and acidified to produce the hydrochloride pigment.(20) The synthetic pathway is shown in Fig. 2.

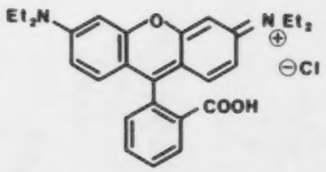

Fig. 1. Structure of major component of R-19.

FDA certification requires that each color lot meet the following specifications(41):

Volatile matter, not more than 5.0 percent.
Water-insoluble matter, not more than 1.0 percent.
Ether extracts (from acid solution), not more than 0.5 percent.
Dimethyl-m-aminophenol, not more than 0.2. percent.
Chlorides and sulfates of sodium, not more than 1.0 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 92.0 percent.

According to an FDA report,(20) the impurities likely to be present include phthalic anhydride, phthalic acid, diethyl-m-aminophenol, resorcinol, o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid, and triethylrhodamine. Side reaction and degradation products were listed as possibly present but in low concentrations. The Environ Report(8) states that possible impurities include the starting materials, phthalic anhydride and diethyl-m-aminophenol, and the intermediate o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid, as well as the subsidiary color, triethylrhodamine. In addition, simple aromatic amines that could be extracted in ether are conceivable. Commercial lots of color contain triethylrhodamine and o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid. An HPLC method with reverse phase chromatography and detection at 230 nm showed the absence of starting materials in commercial colors, but the presence of peaks described as subsidiary colors.(27) Some of the impurities are of toxicological significance since it has been shown that impurities after separation by Thin Layer Chromotography (TLC) are mutagenic by the Ames test.(42)

If the FDA specifications are met and the methods for the determination are sufficiently rigorous for screening purposes, then the levels of these organic impurities should not exceed 2-4% by weight. The likelihood that the total level of impurities is confined to a single compound is low. Most of the impurities seem to be composed of the subsidiary color, triethylrhodamine.(20)

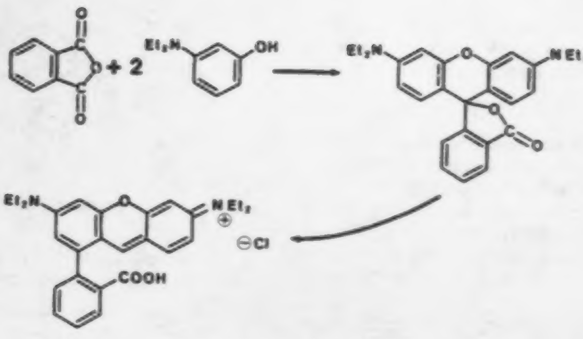

Fig. 2. Synthesis of major component of R-19.

4.2. Short-Term Tests

4.2.1. Mutagenicity

R-19 gave no response in the bacterial Ames tests, using tester strain of *Salmonella typhimurium* TA98 in a sample from FDA,(43) in TA98 or TA1535 using a sample from a major textile firm,(44) or in a sample from Merck Chemical Co. over a wide dose range in TA98 or TA100(45) (a report that the color was inactive in a number of other strains was considered problematical because the color was inhibitory to the bacteria under the conditions used in the assay(46)). Color supplied by the Sigma Chemical Co.(42) or in a rhodamine dye tablet (used to trace water flow),(47) however, was mutagenic in TA98, TA100, and TA1537, as was a lake in TA98, TA1537, and TA1538.(48) The key to understanding these data was provided by the observations that when another color source, with less impurities, was used or the impurity separated by fractionation,(42) the color was not mutagenic, indicating that the positive response seemed to be a result of impurities. In higher organisms, the color did not induce gene conversion in yeast,(49) although there was a weak mutagenic effect when the color (without fractionation) was added to food for *Drosophila*.(50) From these studies it appears that the mutagenic activity of this color is contained in impurities.

4.2.2. DNA Damage/Repair

A *rec* test in *E. coli* was negative,(51) while positive induction of DNA breaks in the *in vitro* Chinese Hamster Ovary cells (CHO) assay was suggested to be related to the lethality of Rhodamine B at the doses used or impurities.(42) The color did not induce gene conversion in yeast,(49) an index of recombinative activity. In CHO cells, DNA damage does occur,(52) but at doses with significant cell lethality.(53) The lethality is not surprising since the color has been shown to be phototoxic, at lower doses, to cultured human skin cells.(54) The CHO studies were conducted using "gold" lights(53) which remove the ultraviolet and blue portion of the spectrum. However, the photoactivation spectrum for the toxic effect of the color is well into the visible region,(54) which would not be removed by "gold" fluorescent illumination. It appears, therefore, that color phototoxicity is an important factor in its ability to damage DNA.

4.2.3. Chromosomal Damage

Chromosomal aberrations were not found in a human cell line at R-19 concentrations up to 10^{-4}M,(55) or in onion root tip or broad bean in culture.(56) However, clastogenic effects were found in Muntjac chromosomes,(57) and CHO cells.(52,58) No induction of bone marrow sister chromatid exchanges (SCE) in the mouse was found at high doses.(59)

For the study with Muntjac cells, the color was obtained from Sigma Chemical Co., a source which was shown to contain mutagenic impurities.(42) It was not purified before use. In one of the positive CHO studies,(52) the color was fractionated before use. However for a significant effect, the dose is approximately at the concentration at which half the cells die (the LC$_{50}$),(53) under conditions of "gold" illumination (discussed above). In the other positive CHO study, cellular toxicity of the color was not reported.(58) However, if it is similar to that seen in the study by Douglas *et al.*,(53) it was appreciable at the effective doses. Therefore, although the color has clastogenic effects, they could be a result either of an impurity in the color or of color toxicity.

4.2.4. Transformation

No reported assays.

4.2.5. Significance

The results suggest that the observed genetic toxicity of R-19 may be a result of noncolored impurities in commercial preparations or may be an indication of R-19 toxicity, especially phototoxicity. Because of this, Rhodamine B should be handled properly when assayed for genetic toxicity.

From the information available in the literature, it is not clear what are the stability characteristics of fractionated color. Fractionated color appears to be nonmutagenic and only damages DNA in doses high enough to induce cell lethality.

4.3. Comparative Toxicology

4.3.1. Negative Studies

Rat: R-19 was fed to Wistar rats (5 male and 5 female) at 4% of the diet for 2 years. No toxic or oncogenic effect was noted.(60)

R-19 was fed to 21 male and female Wistar rats at 0.13% of the diet for 7 months and then at 0.2% in a lifetime study. No significant effects were noted.(61)

R-19 was also fed at 0.008, 0.025, and 0.15% of the diet to groups of 25 male and 25 female SD rats for 104 weeks. Growth suppression was noted in male and female rats at 0.025 and 0.15% levels. Male rats at the 0.008% level also had lower body weights from about the 40th week. There were increases in the thyroid weights and thyroid/body weight ratios.(62)

R-19 was fed to 25 male and 25 female Charles River rats at 0.004% of the diet for 26 months and no adverse effects other than pink coloration of the eyes were noted.(63)

R-19 was fed to Long-Evans rats at 0.04, 0.4, and 4 mg/kg in the diet in a three-generation study, each generation involving 10 males and 20 females at each dose level. No oncogenic effect was noted.(64)

R-19 was fed to CD rats (60 males and 60 females/group in F$_0$ and 70 males and 70 females at F$_1$) in diets containing 0.002, 0.005, and 0.02%. In this two-generation study that continued for 30 months, body weights were somewhat lower in high-dose females.(65)

Dog: R-19 was fed to 3 male and 3 female beagle dogs per group at 0.008, 0.0325, and 0.1% of the diet for 2 years. No oncogenic effect was noted.(66)

Skin Painting: In mice, 0.1. ml of a 1% solution of R-19 was painted twice weekly on the backs of 50 male and 50 female ICR Swiss-Webster mice for 18 months. No oncogenic effect was noted.(67)

4.3.2. Positive Studies

Rats: In CD rats, a multigenerational study similar in protocol and numbers to the one that found no significant effect at 0.02% used 0.075% of R-19 in which the animals were dosed for 132 weeks with *in utero* exposure.(68) Animals receiving 0.075% had a significant reduction in body weight and a significant increase in follicular cell tumors of the thyroid in treated males, both adenomas (12/56 compared to 2/57 for controls) and carcinomas (5/56 compared to 1/57).

Mouse: CD-1 mice (60 animals/sex/group) were dosed at levels of 0.005, 0.02, and 0.1% in the diet for 24 months. Hepatocellular carcinomas were increased in females, up to 19/60 for 0.1% R-19 for adenomas and carcinomas (compared to 4/115 for controls).(69)

4.3.3. Interpretation

Interpretation of the positive rat study:

Toxicology. Rats fed R-19 at 0.075% had moderate weight depression but no effect on survival was seen. Females had more severe weight depression. Toxic lesions in the potential target sites, thyroid and parathyroid glands, were not seen.

Pathology. Increased incidence of thyroid follicular tumors (adenomas and carcinomas) was found in 0.075% males (17/56) as compared with controls (3/57). Five of the dosed males had carcinomas while one control male had thyroid follicular carcinoma. Goiter was not reported. In females, 6/55 dosed rats had thyroid follicular tumors and 2/57 were found in control females. Parathyroid tumors were reported in 9/48 dosed males and 1/44 control males. Few chemicals, if any, cause these parathyroid tumors. Since it is easy to misdiagnose parathyroid hyperplasia (due to renal disease) as neoplasia, these lesions should be reviewed histologically.

Conclusion. This study showed R-19 led to tumors in male rats. More severe body weight depression was noted in females which did not have induced tumors. Goiter was not noted.

The R-19 was obtained from Sun Chemical Corporation as a FDA certified lot, with a stated "purity" of 92%, lot AA-4989. No data were included on the further characterization of the purity of the color additive or the presence of impurities. A later FDA report indicated that lot AA-4989 was 90.3% color, 2.8% volatiles, 0.08% insolubles, and 2.3% triethylrhodamine.(20) A supplementary submitted report(28) showed that lot AA-4989 of the color contained 1.58% triethylrhodamine, expressed as the ratio of triethylrhodamine to R-19 at 554 nm, and about 0.4% other colored impurities, expressed as the ratio of impurities to R-19 at 554 nm. This report did not mention noncolored impurities. From the point of view of chemical purity of the dosing material, the studies were performed in an acceptable manner except for the lack of sufficient data on the purity of the color and the impurities present.

Interpretation of the positive mouse study:

Toxicology. The feeding of diets containing R-19 at a level of 0.1% did not produce effects on body weight gain or mortality. Mild toxic liver lesions were found in mice.

Pathology. Increased incidences of liver tumors were found in both sexes. Dosed males (0.1%) had an incidence of 15/59 as compared with 17/119 in the control males, while 0.1% dosed females had an incidence of 19/60 vs. 4/115 in the control females. More than 50% of the liver tumors in dosed mice of both sexes were malignant.

Conclusion. This study showed that feeding R-19 increased the incidence of liver tumors in female mice. Since no effect was found on body weight gain or survival of both sexes, it is possible that the mice could have tolerated higher doses of R-19. The mild toxic liver lesions in male mice would also support this position.

The chemical analysis of the dosing material used in, and the conclusions of the analysis about, the mouse study were identical to the positive rat study since they were done together.

4.4. Skin Penetration Studies

The *in vitro* studies in human abdominal skin(12) used ^{14}C-labeled R-19 obtained from Amersham Corporation as "side rings-U-(^{14}C)" Rhodamine B, having a specific activity of 38 mCi/mmol (79 μCi/mg). The presumed location of label is shown in Fig. 3.

TLC assays for radiochemical purity, reported by the supplier, using two solvent systems, indicated 95 and 96% purity. Additional TLC assays were also performed.(28) Three TLC bands were separated, scraped, eluted, and counted. The results showed 92.6% Rhodamine B, 5.48% triethylrhodamine, and 1.96% "other" determined from the radioactivity found in eluted bands. When quantitation of the bands was based on absorption at 554 nm, the results showed 97.1% of Rhodamine B, 2.0% triethylrhodamine, and 0.9% "other." Noncolored impurities would not be detected by the latter method. Specific activities calculated on a total weight basis were 85.3 and 81.7 μCi/mg as compared to 79 μCi/mg reported by the supplier.

Radioactive color was prepared in aqueous formulations of different pH, as well as in alcohol, oils, emulsions, and talc. Doses varied from 0.001% in aqueous formulations to 0.5% in talc. Appropriate amounts of ^{14}C were applied to approximately 1 cm^2 of human abdominal skin mounted in the Franz cell with receptor saline solution.

Recoveries from aqueous buffers and emulsions were good with significant retention in the epidermis. Recoveries from oils were also good with significant amounts removed with the first wash. No recoveries were performed with talc.

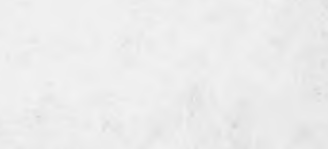

Fig. 3. Presumed location of radiolabel in R-19 major component.

Results showed a 2% pH-related penetration of color in aqueous buffers with smaller penetration in emulsions, oils, and talc. The radiochemical purity was well-defined in the supplementary report.(28) There are still questions as to impurities present and the nature of the ^{14}C component that was found in the receptor cells, but these questions are largely academic and would have a relatively small impact on risk assessment when using the assumptions discussed above.

4.5. Specific Assumptions used in the CTFA R-19 Risk Assessment

- *Assumption 1:* Emulsions are assumed to be absorbed at a rate of 1%/day of the amount applied, which is the rate seen for aqueous solutions. The observed rate of 0.24% may be too low since it was unclear whether (a) the observed rate was the steady state rate; and (b) emulsions in commerce contain the soluble color or the lake.

Validity: Probably invalid, it is easily testable.

Option: Conduct new studies on emulsions for an extended period of time, and include live skin specimens.

Impact: The skin penetrance study(12) shows that the steady state was reached after approximately 60 h. The argument that emulsions contain the color rather than the lake is irrelevant, since the test was performed with the color. Moreover, since it is already questionable whether 3–5 days postmortem skin would retain its original integrity, the assumption of a rate of 1%/day implies a safety factor of 4. The Panel assumed that the absorption rate of colors in emulsions equals 0.25% per day of the amount applied to the skin.

- *Assumption 2:* Since a steady state was not reached with mineral oil as a vehicle, an absorption rate of twice the maximum rate after 3 days is assumed for oil-based products (0.5% for mineral oil and castor oil).

Validity: Unlikely to be correct, it is testable.

Options: (a) Conduct *in vivo* tests in humans and suitable animals; (b) repeat *in vitro* test for extended periods of time with live skin.

Impact: Using twice the absorption rate of mineral oil (0.5%/day) for products based on castor oil is incorrect since the latter rapidly reached a steady-state rate of 0.04%. The assumption implies the application of a safety factor of 12.5. If postmortem artifacts prevent mineral-oil-based colors from reaching the steady state, risk estimates based on the test results are considerably too high. The Panel assumed a reasonable estimate of the mineral-oil absorption rate, given the results in postmortem skin, equal to the observed maximum rate of 0.25% (rounded) and, for castor oil products, no reasons have been found to depart from the observed steady-state rate of 0.04%.

- *Assumption 3:* The absorption rate for aqueous products is assumed to be 1%/day of the applied amount, except for those products that need adjustment.

Validity: Seems correct based on the *in vitro* data.

Impact: The penetrance studies show a range of steady-state absorption rates of 0.82 to 1.03%/day, where 1.03% refers to a 0.001% aqueous solution at pH = 8. Since 0.001% is the maximum concentration of the commercial products and not a median or average, this assumption is one that will probably overestimate the rate. Without other data, however, the Panel accepted use of the CTFA assumption.

- *Assumption 4:* The absorption rate for talc products is 0.002%/day of the amount applied.

Validity: Seems correct based on the *in vitro* data.

Impact: The above rate is a steady-state rate achieved as soon as 2 h after application. Thus, the effect of further deterioration of the skin with time is minimal. The Panel used the CTFA assumption.

4.6. Risk Characterization

4.6.1. CTFA Risk Estimates

From the BIO/DYNAMICS Study in CD-1 Mice. The risk was slightly higher using liver tumors (adenoma or carcinoma) rather than hepatocellular carcinoma only. The estimates of the upper confidence limit on low-dose risk from the linearized model (but not the tumor incidences) were comparable in males and females and, therefore, the tumor data were combined.

From the BIO/DYNAMICS studies in Charles River CD rats. The risk was somewhat higher using thyroid follicular cell tumors (adenoma or carcinoma) rather than carcinoma only. Risk estimates for males and females were similar and, therefore, the tumor data combined.

Table I. Comparison of Risk Estimates of R-19

	Risk(CTFA/90)[a]	Risk(CTFA/Avg)[b]	Risk/90[c]	Risk/Rea[d]
Rat	2.7×10^{-7}	7.1×10^{-8}	1.1×10^{-7}	2.8×10^{-8}
Mouse	1.3×10^{-7}	3.4×10^{-8}	0.5×10^{-7}	1.3×10^{-8}

[a] Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

[b] Risk(CTFA/Avg) is the CTFA risk estimate at "average" estimates of exposure.

[c] Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

[d] Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.

4.6.2. Panel Risk Estimates

Application of the Panel product- and color-specific assumptions above to the usage data(7) results in a total absorbed amount of color of: 0.42 μg/day as an average of the prospective usage survey; 1.62 μg/day as the upper 90th percentile of the prospective survey, as compared to CTFA's estimates of 0.85 μg/day and 3.27 μg/day, respectively. (The factor 0.8 to account for the general assumptions was used.)

4.6.3. Comparison

See Table I.

4.7. Summary

Studies have been conducted on TLC-separated colors that showed some impurities were mutagenic by the Ames test, while the purified color fraction had little indication of mutagenicity. The levels of these impurities may have an impact on R-19 carcinogenicity. However, because of their relatively low concentration, their presence is not likely to alter the risk assessment calculations of risk of the entire color by a significant degree.

Although the risk of R-19 is low, the impurities may be responsible for some of its toxicity. Therefore, it is recommended that the impurities be removed before it is used. It should be possible to develop simple techniques which are cost-effective, and inclusion of a purification step as a criteria for certification, removing those impurities which have significant mutagenic action, would probably reduce an already small risk.

Finally, the color has been shown to be phototoxic. Conditions of its use and the possibility of effects as a result of light exposure should be considered.

5. D&C RED NO. 37 (R-37)

5.1. Chemistry

D&C Red No. 37 (CAS 6373-07-5) (CI 45170:1) (R-37) is an alcohol soluble xanthene color 9-(2-carboxyphenyl)-3,6-bis(diethylamino)-xanthylium octadecanoate (FDA also terms it the 3-ethostearate of 9-o-carboxyphenyl-6-diethylamino-3-ethylimido-3-isoxanthene). Its common name is Rhodamine B stearate and its structure is shown in Fig. 4.(20,70) It is the stearate salt of the same cation as R-19.

R-37 is synthesized from R-19 by treatment with ammonium hydroxide and stearic acid.(70)

FDA certification requires that each color lot meet the following specifications(41):

Volatile matter, not more than 2.0 percent.
Water-insoluble matter, not more than 1.0 percent.
Sulfated ash, not more than 3.0 percent.
Matter insoluble in benzene, not more than 0.5 percent.
Dimethyl m-aminophenol, not more than 0.2 percent.
Stearic acid (not part of the dye), not more than 50.0 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 50.0 percent.

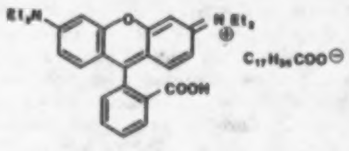

Fig. 4. Structure of major component of R-37.

Therefore, approximately half the molecular weight is taken up by noncolored stearate anion.

FDA(20) describes impurities likely to be present as phthalic anhydride, phthalic acid, diethyl-m-aminophenol, stearic acid, fatty acids related to stearic acid, o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid, and triethylrhodamine. A variety of possible side reaction and degradation products were listed as possibly present, but in low concentrations. The Environ Report(6) does not address R-37, but any impurities are expected to be similar to those reported for R-19. Commercial lots were shown to contain triethylrhodamine, stearic acid, and o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid. Using an HPLC method, an absence of starting materials, and the presence of 6–7 peaks considered to be subsidiary colors has been reported.(27) Some of the impurities are likely to be of toxicological significance since those separated from the closely related R-19 by TLC are mutagenic.(42)

If the FDA specifications are met and the methods for the determination are sufficiently rigorous for screening purposes, then the levels of these organic impurities, less stearic acid when totaled, should not exceed 2–4% by weight. The likelihood that this total level of impurities is confined to a single starting material is low, with most of the impurities seemingly confined to the subsidiary color, triethylrhodamine.(20)

5.2. Short-Term Tests

5.2.1. Mutagenicity

In addition to the information on R-19, R-37 was found not be mutagenic, with or without activation, in TA98, TA100, TA1535, and TA1537.(46)

5.2.2. Other

No additional information.

5.2.3. Significance

R-37 is negative in a mutagenic assay in a laboratory that also found R-19 to be negative. There is no reason to believe that the color will be less contaminated with impurities than the parent R-19, except that the presence of the stearic acid will dilute the contaminant.

5.3. Comparative Toxicology

No long-term animal assays have been performed with this color additive. The presence of the stearate is not likely to affect the toxicological effects of the color once absorbed, except by simple dilution of the cation concentration. It is not clear whether the moiety will decrease gastrointestinal absorption because of decreased water solubility, or increase it as a result of ion-pairing effects.

5.4. Skin Penetration Studies

No skin penetration studies have been performed with this color additive. It is not clear whether the moiety will decrease skin penetrance because of decreased water solubility, or increase it as a result of ion-pairing effects.

5.5. Specific Assumptions Used in the R-37 Risk Assessment

- *Assumption 1:* The information on R-19 can be used to predict the risk from R-37.

Validity: Reasonable and testable. Although it can be assumed that once absorbed, the stearate salt would dissociate to R-19, the issue of concern is the absorption. R-37 might be expected to be more slowly absorbed because of its larger molecular weight and its decreased water solubility. In addition, because of the stearate moiety, certified lots of R-37 only contain about 50% cation by weight compared to more than 92% color for R-19. However, there is a question that ion-pairing effects might alter the absorption rate. Therefore, it is prudent to assume, in the absence of specific information, that the response will be similar to that seen for R-19.

Option: Conduct tests on the toxicity and skin penetrance of R-37.

Impact: The direction and degree of absorption and risk change is not clear. The dilution by the stearic acid will reduce risk by a factor of 2 for the same weight of material. However, if twice as much material (the same amount of "color") is used in applications, this factor will disappear. There is no information on usage of R-37.

5.6. Risk Estimates

5.6.1. CTFA Risk Estimates

CTFA does not estimate risk from this color.

5.6.2. Panel Unit Risk Estimates

Since no color-specific information appears to be available with regard to usage frequency, *in vitro* skin absorption, and commercial formulation, and because R-37 differs from R-19 only in the added stearate moiety, R-19 data on toxicology and skin absorption have been accepted as likely to represent R-37, using a factor of 0.5 for dilution of cation by the R-37 stearate moiety.

It must be appreciated that there is no exposure information (and little toxicological information) for this color, and the risk estimate is based on simple extrapolation from a chemically related color. Thus, the nature of this risk estimate is different from those calculated for R-19, O-17, R-9, and R-3. A risk estimate of 1.3×10^{-7} is actually a unit risk for an absorbed exposure of 0.062 μg/day to R-19-type colors. There is no information on actual human exposure, other than the production of the color is much less than the production of R-19.

5.7. Summary

In the few systems tested, there is no evidence that this color is genetically toxic. It is reasonable to assume that R-37 has the same toxicological effects as R-19, except that the unit risk is divided by approximately two to provide for an equal weight of cation. The unit risk estimates should be used to calculate absolute risks as soon as usage data become available, with absorption studies of color-specific absorption to adjust the risk.

6. D&C ORANGE NO. 17 (O-17)

6.1. Chemistry

D&C Orange No. 17 (CAS 3468-63-1) (CI 12075) (O-17) is a water-insoluble monoazo pigment 1-[(2,4-dinitrophenyl)azo]-2-naphthalenol (also termed 1-(2,4-dinitrophenylazo)-2-naphthalenol by the FDA).

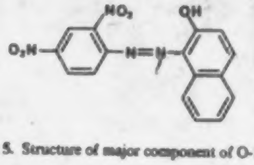

Fig. 5. Structure of major component of O-17.

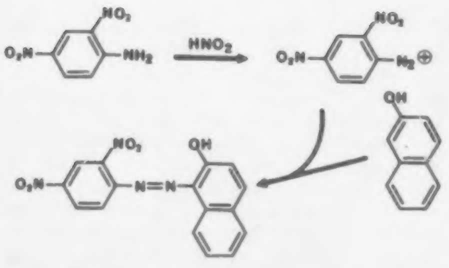

Fig. 6. Synthesis of major component of O-17.

A common trade name is Permanent Orange and its structure is shown in Fig. 5.⁽⁷¹⁾

O-17 is synthesized by the condensation of the diazonium salt of 2,4-dinitrobenzeneamine (2,4-dinitroaniline) with 2-naphthalenol (2-naphthol, beta-naphthol). The synthetic pathway is shown in Fig. 6.(21)

FDA certification requires that each color lot meet the following specifications(41):

Volatile matter, not more than 5.0 percent.
Sulfated ash, not more than 1.0 percent.
Matter insoluble in toluene, not more than 1.5 percent.
2,4-dinitroaniline, not more than 0.2 percent.
Beta-naphthol, not more than 0.2 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 90.0 percent.

FDA(21) describes the impurities likely to be present as 2-naphthalenol (< 0.2%), 2,4-dinitrobenzeneamine (< 0.05%), 4-[(2,4-dinitrophenyl)azo]-1-naphthalenol (< 0.05%), 2-[(2,4-dinitrophenyl)azo]-1-naphthalenol (< 0.005%), 1-[(4-nitrophenyl)azo]-2-naphthalenol (< 0.05%), and possibly a trace of 1-[(2,6-dinitrophenyl)azo]-2-naphthalenol. Other side and degradation products were listed as possibly present, but at trace concentrations. The Environ Report(6) states that the most likely impurities are the starting materials 2,4-dinitrobenzeneamine and 2-naphthalenol, although small quantities of ether-extractable nitroaromatics are conceivable. An HPLC method for the determination of the two starting materials showed much higher levels of 2,4-dinitrobenzeneamine and 2-naphthalenol(22) than by the official FDA cellulose column chromatography method, primarily because the HPLC method solubilized the "insoluble" color and released more impurities trapped in the crystal structure. These results imply a higher level of starting materials in

FDA certified lots than reported by the official method.

Commercial pigment lots were shown to contain the two starting materials and the first three subsidiary colors listed above. The starting material 2,4-dinitrobenzeneamine, a nitroaromatic amine, has been shown to be mutagenic in the Ames test, with and without rat liver S-9 activation.(72)

6.2. Short-Term Tests

6.2.1. *Mutagenicity*

This color is mutagenic in TA98, TA100, TA1535, A1537, and TA1538 with or without S9 activation,(49) with increased activity with microsomal activation except for TA1535. It is also mutagenic whether the source of color is FDA,(43) a major textile firm,(44) in rouge and lipstick,(43,46) or from other sources.(73) Microsomal activation has been shown to increase(49) or inhibit(43-45,73) the response, the difference in reaction to the microsomal mix perhaps reflecting impurities.

In the forward mutation assay using the TK locus in L5178Y mouse lymphoma cells, O-17, from 0.65 to 5 mg/ml, is inactive(74) with and without S-9 activation.

6.2.2. *Other*

There were no data for DNA damage/repair, chromosomal damage or transformation.

6.2.3. *Significance*

This color is a mutagen in bacteria, although not in the one mammalian system tested. There may also be contaminants in the preparation which may be responsible for the difference in the effects of microsomal activation. However, the reduction product 2,4-dinitrobenzeneamine is mutagenic and doesn't require microsomal activation,(72) possibly because the bacteria possess nitroreductases. Azo reduction to a nitrobenzeneamine may be the source of much of the activity. Whatever the source, it is clearly an agent which damages the genome.

6.3. Comparative Toxicology

6.3.1. *Negative or Equivocal Studies*

Mouse: CD-1 mice (60 animals/sex/group) were dosed with 0.025, 0.25, and 1.0% O-17 in the diet for 23–25 months. There was an increase in hepatocellular neoplasms in males, but the increase was not significant.(75)

Rat: O-17 was given at 0.025, 0.1, and 1% of the diet to groups of 25 male and 25 female CD Charles River rats for 104 weeks. Some growth suppression was noted at the higher level. Liver weights were increased in higher dose females. Neoplastic nodules of the liver and hepatocellular carcinomas were increased in females at the 1% dose level, though not significantly.(63)

Dog: O-17 was fed to 3 male and 3 female beagle dogs per group at 0.025, 0.125%, or 1% of the diet for 2 years. In general the treated dogs showed lower body weight gains than controls, however, no significant pathological effects were noted.(66)

Skin Painting Studies: In mice, 0.1 ml of a 1% solution of O-17 was painted on the skin of 50 male and 50 female ICR Swiss-Webster mice twice weekly for 18 months. No oncogenic effect was noted.(67)

0.1 ml of a 1% solution of O-17 was applied weekly to the skin of 50 male and 50 female CF-1 Carworth mice for up to 26 months. No oncogenic effect was noted.(76)

6.3.2. *Positive Study*

Rat: O-17 was given at 1% of the diet initially to F_0 (60 per sex/group) and then the F_1 generation (70/sex/group) of Charles River rats for 26–30 months. This was an FDA-requested study by the same contractor using the same methodology of doses of 0.02, 0.05, and 0.1% of O-17 in diet. Mortality of treated rats was increased over that of controls in the second year. Male rats had an 18% depression in body weight. Pericholangitis was greater in treated male rats killed at 12 months. A similar effect was noted in female rats but at terminal sacrifice the incidence of this lesion was similar in control and treated rats. There was an increase in hepatocellular adenomas in treated female rats at the terminal sacrifice (18 in treated vs. 1 in controls).(77)

6.3.3. Interpretation

Interpretation of the Positive Study—Rats:

Toxicology. There was no weight depression in males fed 1% O-17 until 26–50 weeks. The chemical produced no weight depression in females. No effect on survival was found. Toxic hepatic lesions were seen in females but not in males.

Pathology. Liver tumors (hepatocellular adenoma or carcinoma) were found in increased incidence in females (21/59) fed 1% O-17 as compared with (3/52). The majority of these rats had hepatocellular adenomas while only 4 rats had carcinomas in the 1% group (one animal had both an adenoma and a carcinoma). Two carcinomas, however, were found in female controls. Mammary fibroadenomas were found in increased multiplicity and total numbers in 1% female rats but the incidence of these tumors was not significantly increased (34/59) when compared to controls (28/51).

Conclusion. The liver tumors and toxic liver lesions were found only in female rats. Based on lack of changes in body weight gain and survival these rats may have tolerated higher doses of O-17. The same effect may have been seen on the mammary tumors. However, the study is adequate.

O-17 was supplied by CTFA as FDA certified lot No. AA 6260 and listed as "97% pure." No data were included on the further characterization of the purity of the color additive or the presence of impurities. Certified FDA lots should contain less than 0.2% of the starting materials; however, analysis of this lot showed 0.29% 2,4-dinitrobenzeneamine and 0.70% 2-naphthalenol when analyzed by the HPLC method.(22) The study seems to be well-controlled but lacks definitive information on the purity of the color and the levels of impurities that may be present.

Interpretation of the Equivocal Mouse Study:

Toxicology. Feeding of dietary levels of 1% of O-17 produced no depression in body weight gain. In the males, however, there was an effect of dose on survival. The cause of this increased mortality was not reported but toxic lesions were induced such as pigmentation in various tissues and myocarditis.

Pathology. There was an equivocal increase in liver tumors in high-dose male mice.

Conclusions. Increased mortality and toxic lesions were found in male mice, but this study does not provide definitive evidence for carcinogenicity in mice.

The chemical analysis of the lot of color was the same as that in the rat study since they were done together.

6.4. Skin Penetration Studies

The *in vitro* study(13) used ^{14}C-D&C Orange No. 17 obtained from Amersham, UK as 2,4-dinitro [U-^{14}C]phenylazo-2-{1,4,5,8-(^{14}C)}-naphthalenol with a reported specific activity of 5.6 mCi/mmol. The ^{14}C label is distributed as shown in Fig. 7.

The supplier stated that the synthesis method used insures an equal contribution of the specific activity from each labeled part of the molecule. Data were supplied indicating that the radiochemical purity was 95 and 96% determined by TLC separation in two solvent systems. The presence of subsidiary colors or the identification of the remaining 4–5% of the radioactivity was not stated. Dose formulations were prepared in oils and cream blusher at 0.6% color and in talc at 5% color. Approximately 1.5×10^6 DPM of color was applied in oils, 4.7×10^6 in cream blusher, and 38×10^6 in talc. Volpo 20 was used in the receptor cell to aid solubilization of the pigment. Recoveries of 80–90% were seen in oil formulations and 40–50% in cream blusher. Recoveries were not addressed in the talc studies. Most of the dose was removed with toluene skin washes, although ^{14}C was found in all skin preparations. Counting efficiencies were not stated.

This study used color formulations of defined radiochemical purity; however, the nature of the 4–5% impurity was not addressed. The question of solubility of the color in the receptor solution was adequately discussed. The rate of penetration through the skin was low. A concern can be raised that if the radioactive impurity was all 2,4-dinitrobenzeneamine (4–5% of the ^{14}C), it might be preferentially absorbed by the skin. Since, however, skin absorption of ^{14}C was less than 0.03% of the amount applied/day in liquid media and less than 0.001% of the amount

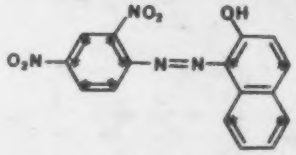

Fig. 7. Location of Radiolabel in major component of O-17.

applied/day in talc formulations, it is unlikely that this impurity would have a significant impact on risk assessment calculations because of the generally small amount of material that penetrates.

6.5. Specific Assumptions Used in the CTFA O-17 Risk Assessment

- *Assumption 1:* For creams and oils the absorption rate is 0.01%/ day.

Validity: Unknown but testable. However, for insoluble materials, the interpretation of these rates is not simple.

Option: Conduct a live skin test for longer periods of time.

Impact The skin test revealed rates of 0.003–0.007% of applied amount/24 hours, implying an overestimation of the absorption by a factor of 2. However, the real factor is unknown because it is not clear whether the above rates refer to a maximum rate or a steady-state rate. The Panel assumed an absorption rate of 0.005%/day of the amount applied, half that assumed by CTFA.

- *Assumption 2:* The absorption rate for O-17 in talc is 0.001%/day of the amount applied.

Validity: Probably correct and testable.

Options: Repeat *in vitro* skin studies with live skin models.

Impact: CTFA mentioned 0.001% absorption in its text,(3) citing the skin penetrance study(13) and printed 0.00009% in a table. The penetrance study uses the values 0.001%. The laboratory data sheets are difficult to interpret, therefore the Panel used 0.001%.

- *Assumption 3:* The use of Volpo 20 in the receptor of the Franz cell will not significantly alter the skin penetration.

Validity: Probably valid and testable. *In vivo* there are a number of factors, such as protein binding in blood flowing through the capillary bed, which would remove the color when it passed through the skin "solubilizing" the color, which was the reason for using the Volpo 20.

Option: Conduct parallel studies *in vivo* and *in vitro* using saline and 6% Volpo 20.

Impact: Use of Volpo 20 may result in higher observed skin penetrance rates. However, the effect on the exposure is not likely to be significant since total penetrance using Volpo 20 was extremely low. The Panel accepted use of the CTFA assumption.

6.6. Risk Characterization

6.6.1. *CTFA Risk Estimates*

From the BIO/DYNAMICS Study in CD-1 Mice. Data from an equivocal study were treated by the Panel as if it was positive, since it was done so in the CTFA risk assessment, and a comparison to the CTFA estimate was thought useful. Risk estimates were slightly higher using liver tumors (adenoma or carcinoma), rather than hepatocellular carcinoma only. Males were more sensitive than females.

From the BIO/DYNAMICS Studies in Charles River CD Rats. The risk estimate was based on liver tumors in females. Data from two very similar studies were combined to provide two dose levels plus controls.

6.6.2. *Panel Risk Estimates*

Application of the product- and color-specific assumptions to these usage data results in a total absorbed amount of color per day of 0.00189 μg/day as an average of the prospective survey; 0.00635 μg/day as the upper 90th percentile of the prospective survey. The comparable amount calculated by CTFA assumptions for the upper 90th percentiles is 0.0208 μg/day.

The factor 0.8 accounted for the effect of the general assumptions.

6.6.3. *Comparison*

See Table II.

Table II. Comparison of Risk Estimates of O-17[a]

	Risk(CTFA/90)[b]	Risk/90	Risk/Rea
Rat	2.1×10^{-10}	5.1×10^{-11}	1.5×10^{-11}
Mouse	0.7×10^{-10}	1.7×10^{-11}	0.5×10^{-11}

[a] Note that CTFA does not give an average exposure estimate for O-17.

[b] Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

[c] Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

[d] Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable ~~estimate of exposure.~~

6.7. Summary

The animal studies were properly controlled except for a lack of data on the purity of the color (subsidiary color) or on the levels of impurities, at least one (2,4-dinitrobenzeneamine) of which is a potent mutagen. If this color were certified according to FDA specifications with the cellulose column chromatography method, the level of free amine should not exceed 0.2%. However, an HPLC method showed that the level of free amine was 0.29% in this lot. The HPLC method, with its more vigorous solubilization of "insoluble" color would result in the detection of higher levels of impurities than would be reported by the official certification method.

The level of impurities may have an impact on risk assessment only if the degree of potency of the impurities is substantially greater than that of the color. Based on the strong mutagenicity of O-17 without activation in several strains, the mutagenicity of the azo reduction product, and the reported mutagenicity of 2,4-dinitrobenzeneamine with or without activation, it is unlikely that the carcinogenic "potency" differs from the parent compound by several orders of magnitude.

It is important not to ignore the definite mutagenicity of the agent and its metabolite in bacteria. Because the chemical is only slightly soluble, one can speculate that the extent of absorption by the gut may be small; however, the role of intestinal bacterial enzyme activity, such as azo reductase on the azo bond, in producing soluble products should not be ignored. Possible slow absorption may be a factor in the weak carcinogenic response, and the risk assessment figures should be used cautiously with this genetically toxic agent.

7. D&C RED NO. 9 (R-9)

7.1. Chemistry

D&C Red No. 9 (CAS 5160-02-1) (CI 15585:1) (R-9) is a water-insoluble monoazo color additive which is the barium salt (2:1) of 5-chloro-2-[(2-hydroxy-1-naphthalenyl)azo]-4-methylbenzenesulfonic acid (FDA also terms it the barium salt of 1-(4-chloro-o-sulfo-5-tolylazo)-2-naphthalenol). It is commonly used as pure color and in a lake form. Its structure is shown in Fig. 8.(78)

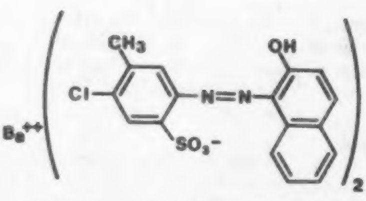

Fig. 8. Structure of major component of R-9.

R-9 is synthesized by diazotization of Red Lake C amine and coupling with 2-naphthalenol to produce D&C Red No. 8 (R-8). This color additive is then treated with barium chloride to produce the barium salt of R-8, known as R-9. The synthetic pathway is shown in Fig. 9.(23)

FDA certification requires that each color additive lot meet the following specifications(41):

Volatile matter, not more than 5.0 percent.
Ether extracts (isopropyl ether), not more than 0.5 percent.
Red Lake C Amine, not more than 0.2 percent.
Beta-naphthol, not more than 0.2 percent.
Chlorides and sulfates of sodium, not more than 6.0 percent.
Oxides of iron and aluminum, not more than 1.0 percent.
Pure dye (as determined by titration with titanium trichloride), notless than 87.0 percent.

The methods of analysis for the two starting materials are for soluble impurities only and may underestimate the levels of impurities trapped within the crystal structure of this insoluble color.(23)

FDA(23) describes the impurities likely to be present as Red Lake C Amine (2-amino-5-chloro-4-methylbenzenesulfonic acid) and its many possible isomers and impurities unique to each synthetic method, 2-naphthalenol, and the barium salt of 4-(4-chloro-2-sulfo-5-tolylazo)-1-naphthalenol (also termed 4-naphtholazobenzene-4-methyl-5-chloro-1-sulfonate) (a subsidiary color). Other nitroaromatics, subsidiary colors, by-products, and degradation products were also listed as possibly present. The Environ Report(6) states that, in addition to the two starting materials, other likely impurities are 4 related subsidiary colors. Also, impure isomers of the starting amine may be present in small quantities. Unsulfonated aromatic amines could conceivably be present in isopropanol extractables, but at very low concentrations. Commercial color lots were shown to contain the starting materials and the subsidiary colors listed above.

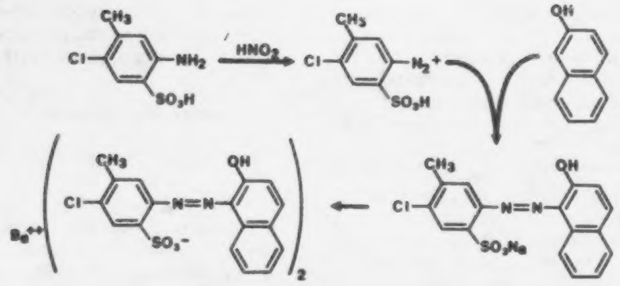

Fig. 9. Synthesis of major component of R-9.

Naganuma *et al.*(29) defined a good methodology to investigate the possible impurities in R-9, including positional isomers of the starting materials and the subsidiary colors produced from these isomers. The data show that the majority of the impurities present in R-9 can be attributed to the impurities present in Red Lake C Amine. Analysis of four lots of R-9 from US manufacturers showed that these amine impurities were present at 30–84 ppm. (Note: The colors analyzed by Naganuma were *not* used in the bioassays.) This paper also proposed a cost-effective method of synthesis of relatively pure Red Lake C Amine and R-9, scaled up for commercial use. The major change involves a purification of the Red Lake C Amine prior to diazotization and coupling with 2-naphthalenol. Other investigators reported 0.1–0.5% 4-(4-chloro-2-sulfo-5-tolylazo)-1-naphthalenol in three commercial samples of color from the US.(30)

A supplemental report(31) partially answered the questions of color additive purity (i.e., the presence of impurities, starting materials, and subsidiary colors) in the color lot used in the NCI rat bioassay(79) and the skin penetration study.(14) An HPLC method was utilized to separate impurities using detection at 254 and 490 nm, in which a substance must absorb at both wavelengths to be detected. Thus, this method was only able to evaluate colored impurities.

The color lot used in the bioassay (FDA Certified lot no. Z8054, 89.8% color) was found to be 98.8% "pure" (area percent) with several other colored bands reported. Amine and non-azo impurities would not have been detected. The ^{14}C-labeled color used in the skin penetrance studies (Amersham-U-(^{14}C)-R-9) was also analyzed by the HPLC method and found to be 99.1% R-9 with 4 other colored bands. When analyzed for radiochemical purity, 95.6% of the radioactivity was associated with R-9, with eight other radioactive bands including Red Lake C Amine, and two other non-azo compounds.

This study was not designed to look at noncolored impurities; however, the color purity is better defined than by the nonchromatographic FDA certification method. One also questions why the data derived from a TLC method previously described(31) were not presented. Other investigators(29) have done definitive work with TLC.

7.2. Metabolism

Two radiolabeled preparations have been synthesized; one labeled with ^{14}C in the benzene ring and the other labeled with ^{14}C in the naphthalenol ring. After administration of either preparation added to the diet in a concentration of 3000 ppm (0.3% of the diet) about 54 of the dose of the ^{14}C-naphthalenol label and about 35% of the dose of ^{14}C-benzene label were excreted into urine within 48 h.(81) The compound is insoluble in water and there is no evidence that there would be a dose-dependentrate of dissolution of the compound in the gastrointestinal tract. Very little of the parent compound could be detected in the urine; instead, the radiolabel in the urine appeared to be associated predominantly with three metabolites. One of the metabolites containing the ^{14}C-naphthalenol label was tentatively identified as 1-amino-2-naphthalenol and the other as an unidentified conjugate. The principal metabolite containing the ^{14}C-benzene label was tentatively identified as Red Lake C Amine. Both metabolites would be expected on reduction of the azo-group. However, it is not clear whether the reduction occurred predominantly in the gastrointestinal tract and the metabolites were then absorbed or whether the parent compound was absorbed and then eliminated in the liver predominantly by azoreduction and biliary excretion. Unfortunately, the experiments were not designed to evaluate the two mechanisms or to determine the bioavailability of the compound.

Some of the ^{14}C-naphthalenol label appears to be covalently bound to erythrocytes, possibly through the formation of a chemically reactive metabolite of the 1-amino-2-naphthalenol. Although the investigators suggest that the binding of the metabolite to erythrocytes might lead to the destruction of the erythrocytes in the spleen and thereby cause splenic injury, the hypothesis has not been adequately explored. Nevertheless, the fact that neither R-8 nor R-9 are mutagenic in bacterial systems (see below) suggests that the reactive metabolite formed from 1-amino-2-naphthalenol does not rapidly combine with DNA. This compound is not mutagenic in bacteria. However, a number of the colors which are reduced to this compound (such as O-17) are mutagenic, implying that the other amines such as 2,4-dinitrobenzeneamine generated may account for the mutagenicity of these other colors.

7.3. Short-Term Tests

7.3.1. Mutagenicity

R-9 was negative in TA98, TA100, TA1535, and TA1537, with and without S9 activation,(68) and R-9 lake from another source was inactive in the same strains, plus TA1538.(69)

7.3.2. DNA Damage/Repair

R-9 supplied by CTFA did not induce DNA synthesis over a wide dose range *in vitro* or after *in vivo* activation at high doses using hepatocytes.(82)

7.3.3. Other

There were no data from chromosomal damage or transformation assays.

7.3.4. Significance

There is no evidence of mutagenicity in bacteria for this color or induction of DNA synthesis in hepatocytes. Other systems have not been tested. There is no evidence for genetic toxicity of this color either by itself or as part of a lake.

7.4. Comparative Toxicology

7.4.1. Negative Studies

Rat: R-9 was given at 0.01, 0.05, 0.25, and 1% of the diet to 25 male and 25 female Osborne-Mendel rats for two years. Although no oncogenic effect was noted, splenomegaly and other splenic lesions were noted, especially in rats on the two highest dose levels.(83)

Groups of 60 male and female and then 70 male and female (2nd generation) Charles River SD rats received 0.01, 0.02, or 0.05% of R-9 in the diet in a two-generation study for a period up to 30 months.(80)

In a second study on a similar protocol (the LBI study), 70 male and female rats were fed 1.0% of the color additive following *in utero* exposure. Splenic lesions were noted in the male rats fed 1% of R-9.(80)

Mouse: In the NCI study, R-9 was given at 0.1 or 0.2% to groups of 50 male and 50 female B6C3F1 mice for 103 weeks. At the high dose there was a minimal change in body weight. No oncogenic effect was noted.(84)

Charles River CD-1 mice (60 male and 60 females at each level) received 0.005, 0.025, or 0.1% of R-9 in the diet for 24 months. Neoplastic effects were not noted.(80)

In a second study (the LBI study) 60 male and 60 female CD-1 mice received 0.2% of R-9 for 22 months. Neoplastic effects were not noted.(80)

Skin Painting: In 50 male and 50 female ICR Swiss-Webster mice 0.1 ml of a 1% solution or suspension of R-9 was applied twice weekly to the skin for 18 months. No oncogenic effect was noted.(67)

One-tenth ml of a 1% solution of R-9 was applied weekly to the skin of 50 male and 50 female CF-1 Carworth mice for 26 months. No oncogenic effect was noted.(76)

7.4.2. Positive Study

Rat: In the NCI study, R-9 was given at 0.1 or 0.3% in the diet to 50 male and 50 female F344 rats in each group for 103 weeks. Females at the higher dose level showed a 6% weight depression compared to controls. Splenic sarcomas and neoplastic nodules of the liver were increased in male rats.(84)

7.4.3. Interpretation

Interpretation of positive study:

Toxicology. R-9 in F344 rats produced no effect on survival when fed at dietary levels of 0.3%, but toxic lesions were found in the spleen of male and female rats. These toxic lesions have been described in rats fed diets containing aniline, azobenzene, dapsone, and other aromatic amines.(83)

Pathology. Splenic sarcomas were found in 26/48 male rats fed 0.3% R-9 and in 0/50 control males. These were highly malignant, unusual tumors and several metastasized to peritoneal sites. None were seen in female rats fed R-9.

Hepatic neoplastic nodules were found in 7/49 high dose (0.3%) male rats and 6/50 low dose (0.1%) rats and 0/50 control males. High dose (0.3%) female rats had 5/50 nodules while controls had 1/50.

Conclusion. R-9 was carcinogenic in male F344 rats and also produced splenic toxic lesions associated with the induced splenic sarcomas. The mechanisms responsible for these tumors are unknown, but they are induced by some aromatic amines and related compounds.(64) All may produce methemoglobinemia. This study was adequate for determining the carcinogenicity of R-9 in F344 rats.

The rats were housed together in plastic-bottomed cages. R-9 was obtained from H. Kohnstamm & Co. as FDA certified lot Z-8054, 89.8% color. One peak was seen in an HPLC chromatogram. Other assays performed to characterize the color were elemental analysis, water content (1.58%), IR (consistent with standards), UV (no reference spectra), and TLC. Two TLC systems were used, one detected three impurities, the other 5 impurities. Detection was by visible and UV visualization. The nature of the impurities seen by TLC was not stated. Results from the FDA analysis showed 87% color, 1.8% volatile matter, 0.15% 2-naphthalenol, and less than 0.015% Red Lake C Amine.(108) The dosing seemed to be well-controlled.

One criticism of this study was the group housing of the rats in solid-bottom cages where rats could ingest feces likely to contain the metabolites of the color produced by the azo-reductases of the GI tract. Some of these aromatic amines are established human carcinogens, others are suspect human carcinogens. The amount of coprophagy was likely to be small as animals had access to feed and water at all times. Nevertheless, there is the possibility that potentially carcinogenic aromatic amine metabolites could have been ingested.

7.5. Skin Penetration Studies

The *in vitro* studies on R-9(14) used ^{14}C-R-9 obtained from Amersham, UK, labeled on the "benzene" ring, presumably on the Red Lake C Amine ring. The stated specific activity was 10.6 mCi/mmol. No data were supplied in the penetrance study on the radiochemical purity; however, the supplemental report showed a radiochemical purity of 95.6%, with 8 other radioactive fractions seen, including Red Lake C Amine and two other non-azo compounds.(31)

Formulations were prepared in oils and talc at 5% color and dosed as 3 μCi/5 μl/cm^2. A cream blush formulation was prepared at 0.5% and dosed at 1.5 μCi/25 μl/cm^2. Approximately 3–4 million DPM of ^{14}C was applied in each preparation. Volpo 20 was used in receptor cells to aid the solubility of the color. Most of the material was found in skin washings with good overall recovery of ^{14}C. Counting efficiencies were less than 30% because of the large amount of aqueous fraction counted in the gelled counting cocktail.

The experimental design seems sound with the exception of the lack of information on radiochemical purity and impurity levels, partially addressed by the supplemental report. Characterization of the identity of the separated impurities would have aided risk assessment deliberations.

7.6. Specific Assumptions Used in the CTFA R-9 Risk Assessment

- *Assumption 1:* The absorption rate for R-9 is 0.06%/day of the applied amount, except for those products that need adjustment (e.g., nail polish).

Validity: Would be reasonable if the above rate is a steady-state absorption rate. Although the penetrance study report(14) indicated that no steady state was reached, the data indicate a plateau for split-thickness skin chambers with castor oil and cream as vehicles—hence, a steady-state rate. The data provided indicate that absorption values ranging from 0.016 to 0.064%/day were reached after 2 days. The Panel accepted use of CTFA's estimate.

- *Assumption 2:* The use of Volpo 20 in the receptor of the Franz cell will not significantly alter the skin penetration.

Validity: Probably valid and testable. *In vivo* there are a number of factor's, such as protein binding in blood flowing through the capillary bed, which would remove the color when it passed through the skin, and thereby "solubilizing" the color that penetrates.

Option: Conduct parallel studies *in vivo* and *in vitro* using saline and 6% Volpo 20.

Impact: Use of Volpo 20 may result in higher observed skin penetrance rates. The effect is not likely to be significant for the risk estimate. The Panel used this assumption.

- *Assumption 3:* 50% of the amount of lipstick applied will be swallowed.

Validity: Unknown but testable.

Option: Conduct a study in women on the amount of lipstick swallowed using a radiochemically labeled color or other tracer. Include measurement of the amount lost due to contact of the lips with other surfaces or to wiping off.

Impact: The Panel agrees with CTFA that 50% is likely to be an overestimation. Since specific data for adjusting the percentage swallowed are not available, however, the Panel accepted use of CTFA's estimate.

7.7. Risk Characterization

7.7.1. CTFA Risk Estimates

From the NCI rat study: The most sensitive carcinogenic end-point was splenic tumors in males.

7.7.2 Panel Risk Estimates

Information on the usage frequency indicates that R-9 is present in 6 groups of products. Application of the color- and product-specific assumptions to the usage data results in a total absorbed amount of:

1.211 μg/day as an average of the retrospective usage survey;

1.716 μg/day as the upper 90th percentile of the retrospective survey, as compared to the CTFA estimate of 3.44 μg/day.

For ingestion, the use of the color- and product-specific assumptions and the values of application frequency and amount per application given by CTFA leads to an ingested amount:

86 μg/day as an average based on a survey of ingested lipstick;

415 μg/day as the upper 90th percentile

Both figures are similar to CTFA.

Table III. Comparison of Risk Estimates for R-9[a]

	Risk(CTFA/90)[b]	Risk/90[c]	Risk/Res[d]
External	4.3×10^{-8}	1.7×10^{-8}	1.2×10^{-9}
Ingested	5.1×10^{-6}	4.3×10^{-6}	8.9×10^{-7}

[a] Note, CTFA did not calculate risk estimates based on average exposure levels.

[b] Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

[c] Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

[d] Risk(Res) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.

As discussed earlier, it is believed that the prospective survey is less biased than the retrospective study. No results, however, have been provided from the prospective survey so the retrospective study data are used. Appropriate factors 0.8 and 6/7 were used to account for the general assumptions.

7.7.3. Comparison

As shown in Table III, the risk from ingestion does not include the risk due to absorption of R-9 through the lip surface. Since the skin absorption rate of any of the tested vehicles was less than 0.1%, the incremental risk from absorption through the lip surface would be orders of magnitude lower than the risk from ingestion.

7.8. Summary

The NCI study is complicated by the possible ingestion of fecal metabolites. The analyses of color do not define the levels of non-azo impurities. Both effects are not likely to produce large changes in the risk assessment calculations.

For the skin studies 95.6% of the radioactivity was associated with the R-9 peak, with 8 minor peaks including some non-azo material and some starting material. The radiochemical purity seems to be sufficient so that the risk assessment calculations are not significantly altered.

As a final word of caution, the risk estimates are based on a recent usage survey and any increase or decrease in the color usage will result in proportionate changes in the estimate of risk. Also, it is merely a CTFA recommendation to limit the dye to 2% in lipstick as it is used in the CTFA risk assessment (FDA regulations allow 3%). It is not binding, however, and exceeding it could lead to an increase in the risk (however, because of the insolubility of the compound, especially as a lake, an increase in concentration may be meaningless).

8. D&C RED NO. 8 (R-8)

8.1. Chemistry

D&C Red No. 8 (CAS 2092-56-0) (CI 15585) (R-8) is a sparingly soluble monoazo color additive which is the monosodium salt of 5-chloro-2-[(hydroxy-1-naphthalenyl)azo]-4-methylbenzenesulfonic acid (FDA also terms it the monosodium salt of 1-(4-chloro-o-sulfo-5-tolylazo)2-naphthalenol). It is commonly used as pure color and as lakes. Its structure is shown in Fig. 10.(87) It is the sodium salt of R-9.

R-8 is synthesized by diazotization of Red Lake C amine and coupling with 2-naphthalenol. The synthetic pathway is identical to that shown above for R-9 except for the last step.(23)

FDA certification requires that each color additive lot meet the following specifications(41):

Volatile matter, not more than 10.0 percent.
Ether extracts (isopropyl ether), not more than 0.5 percent.
Red Lake C Amine, not more than 0.2 percent.
Beta-naphthol, not more than 0.2 percent.
Chlorides and sulfates of sodium, not more than 5.0 percent.
Mixed oxides, not more than 1.0 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 85.0 percent.

FDA(23) describes the impurities likely to be present as Red Lake C Amine (2-amino-5-chloro-4-methylbenzenesulfonic acid) and its many possible isomers and impurities unique to each synthetic method, 2-naphthalenol, and 4-(4-chloro-2-sulfo-5-tolylazo)-1-naphthalenol (a subsidiary color). A wide variety of nitroaromatics, possibly subsidiary colors, by-products, and degradation products were also listed as possibly present. The Environ Report(6) does not address R-8, but impurities could be expected to be similar to those described for R-9. Commercial color lots were shown to contain the starting materials and the subsidiary color listed above.

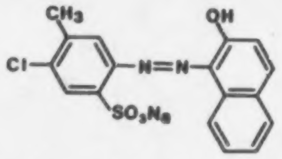

Fig. 10. Structure of major component of R-8.

8.2. Short-Term Tests

8.2.1. *Mutagenicity*

In addition to the work reported for R-9, R-8 itself was negative in TA98, TA100, TA1535, and TA1537, with and without S9 activation.(46) R-8 supplied by FDA was also negative in TA98 as was the color as part of a lipstick preparation.(43)

8.2.2. *Other*

There were no reports for DNA damage/repair, chromosomal damage or transformation.

8.2.3. *Significance*

The effects of this color in short-term tests are expected to be similar to R-9, since the only difference is the cation. There is no evidence for mutagenicity in bacteria for R-8. Other systems have not been tested. There is no evidence for genetic toxicity of this color, either by itself or as part of a preparation.

8.3. Comparative Toxicology

No long-term animal assays have been performed with this color additive. However, there is little reason to suspect that the material would be different toxicologically from R-9 once it was absorbed. When the color reaches the stomach, it is highly unlikely it is maintained as the sodium salt, and R-8 and R-9 are likely to be similar, if not identical, ionic forms in the gut.

8.4. Skin Penetration Studies

Skin penetration studies have not been performed with this color additive. The increased water solubility may increase skin penetrance of R-8 compared to R-9 when both are used as pure color. However, when both color additives are used as lakes, there is not likely to be any difference in solubility and, thus, skin penetration would be expected to be nearly identical.

8.5. Specific Assumptions Used in R-8 Risk Assessment

- *Assumption 1:* The information on R-9 can be used to predict the risk from R-8.

Validity: Reasonable and testable. The risk assessment performed on the closely related color additive, R-9, may have some relevance to R-8. R-8 is a sodium salt and is more soluble than R-9. There is no R-8 exposure information.

Option: Conduct testing on the toxicity and absorption of R-8.

Impact: The increased solubility may increase penetrance.

8.6. Risk Characterization

8.6.1. CTFA Risk Estimates

CTFA made no estimates of risk from this color.

8.6.2. Panel Unit Risk Estimates

R-9 is a barium salt and R-8 is the sodium salt of the same anion. Given the highly acid milieu of the stomach, there would be no reason for assuming that R-8 would behave differently from R-9 with regard to the cancer response to oral dosing. Once absorbed, therefore, it is reasonable to assume an equal toxicity and an equal dose-response curve.

With regard to absorption through the skin there are differences between the two colors with regard to their solubility in water. However, it remains unclear whether such differences would have any impact on the absorption rate if R-8 would have been tested at prevailing concentrations in vehicles compatible with marketed products.

It must, however, be understood that there is no exposure information for this color, and the unit risk estimate is based on simple extrapolation from a chemically related color.

Thus, the nature of this risk estimate is different from those calculated for R-19, O-17, R-9, and R-3. This risk estimate is actually a unit risk, similar to R-37, of 4.3×10^{-8} for an absorbed dose of 3.44 μg/day to R-9 type colors. There is no information on actual human exposure, except, based on production data of the colors, that it is probably less than R-9.

8.7. Summary

The few tests for genetic toxicity that have been performed have been negative. Since it is reasonable to assume that R-8 has the same toxicological effects as R-9, any difference in the risk is probably related to any differences in exposure. The unit risk estimates should be used whenever exposure estimates are available to calculate absolute risk.

9. FD&C RED NO. 3 (R-3)

9.1. Chemistry

FD&C Red No. 3 (CAS 16423-68-0) (CI 45430) (R-3) is a water soluble xanthene dye 3′,6′-dihydroxy-2′,4′,5′,7′-tetraiodo-spiro[isobenzofuran-1(3H), 9′-[9H]xanthene]-3-one, disodium salt, (known also by the FDA as "principally the monohydrate of 9(o-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthene-3-one, disodium salt, with smaller amounts of lower iodinated fluoresceins"). Its common name is erythrosine and its structure is shown in Fig. 11.(24)

R-3 is synthesized by the condensation of phthalic anhydride and resorcinol. The intermediate product 2-(2′,4′-dihydroxybenzoyl)benzoic acid is condensed with another mole of resorcinol to produce fluorescein. The fluorescein is then iodinated to produce R-3. The synthetic pathway is shown in Fig. 12.

FDA certification requires that each color additive lot meet the following specifications(41):

Volatile matter, and chlorides and sulfates (calculated as the sodium salts), total not more than 13 percent.
Water-insoluble matter, not more than 0.2 percent.

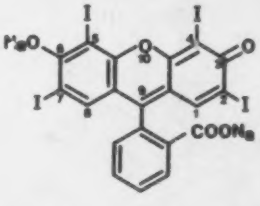

Fig. 11. Structure of major component of R-3.

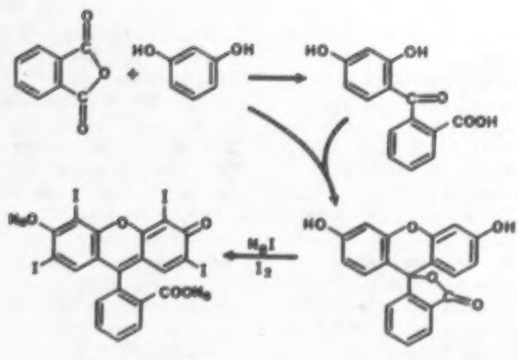

Fig. 12. Synthetic pathway of major component of R-3.

Unhalogenated intermediates, total not more than 0.1 percent.
Triiodoresorcinol, not more than 0.2 percent.
2-(2′,4′-Dihydroxy-3′,5′-diiodobenzoyl)benzoic acid, not more than 0.2 percent.
Other lower iodinated fluoresceins, not more than 9 percent.
Lead (as Pb), not more than 10 parts per million.
Arsenic (as As), not more than 3 parts per million.
Total color, not less than 87 percent.

The starting materials and intermediates are possible impurities as well as triiodinated fluorescein. Two reports(6,24) suggest that the following impurities and subsidiary colors may be present: phthalic acid, phthalic anhydride, resorcinol, 2-(2′,4′-didydroxybenzoyl)benzoic acid, iodine, sodium iodide, 2-(2,4-dihydroxy-3′,5′-diiodobenzoyl)benzoic acid, triiodoresorcinol, 2,4,7-triiodofluorescein, 2,4,5-triiodofluorescein, 4,5-diiodofluorescein, 2,5-diiodofluorescein, 4-iodofluorescein, 2-iodofluorescein, and fluorescein. Other impurities are possible, depending on the purity of the starting materials. HPLC chromatograms obtained from FDA showed the separation of subsidiary colors at 436 and 546 nm.(25) Of the 5–8 peaks seen, R-3 was always the predominant peak with 2,4,5-triiodofluorescein the predominant subsidiary color. Other subsidiary colors identified in "commercial" lots were 2,4,7-triiodofluorescein, 2,7-diiodofluorescein, and a series of small peaks identified as "group." In the chromatograms examined, R-3 was present at 90–94% of the colors detected at the two visible wavelengths. Two reports examined "Erythrosin B" and "Erythrosine" for the presence of subsidiary colors and impurities. Commercial samples of "Erythrosin B" from eight suppliers in the UK were examined using TLC and were found to contain numerous colored bands (subsidiary colors) as well as several bands detected with 254 nm UV light. Major subsidiary colors identified were 2,4,5-triiodofluorescein, 2,4,5-triiodo-4′,5′,6′,7′-tetrachlorofluorescein, 4,5-diiodofluorescein, and 4-iodofluorescein. None of the UV absorbing bands were identified.(32) Three samples of commercial "Erythrosine" from Japanese suppliers, were examined by HPLC using reverse-phase chromatography and detection at 230 nm. The results showed the absence of starting materials, except for traces of phthalic acid in one lot, and the presence of 2–3 unidentified subsidiary colors.(27) No quantitative data or definitive analyses of impurities were given.

9.2. Metabolism

After intravenous administration to rats, R-3 is rapidly eliminated predominantly into bile. The clearance by way of the bile was about 55 times that into urine. Ultimately, most of the compound is excreted into the feces. At one time it was thought that high protein bound iodine in blood plasma might reflect the metabolism of the color by a deiodination reaction, but further study revealed that the substance was the color rather than thyroxine.(99) Although there is no definitive evidence that the substance is converted to other metabolites, the possibility that small amounts of the compound undergo metabolism can never be completely excluded. Nevertheless, the finding that R-3 is not a mutagen in bacteria may support the view that it is not converted to chemically reactive metabolites that react with DNA, but certainly does not preclude such reactions in other systems. Since the predominant route of elimination is the bile, much of the compound absorbed from the gastrointestinal tract may be returned to the intestine by way of the bile before it enters the systemic circulation. The finding that substantial amounts of the unchanged substance are excreted into feces is not necessarily indicative of dose-dependent absorption. The data are not sufficiently complete, however, to estimate hepatic extraction ratios and, thus, the relative steady-state concentrations in the gastrointestinal tract, the liver, the systemic blood, and extrahepatic organs remain unknown. Nevertheless, we may anticipate that if the compound is as readily excreted in bile of humans, as it is in rats, that the largest area under the curve (*AUC*) of the aqueous concentration of the compound used as a cosmetic will be in the skin. The aqueous phase of the cells in the thyroid should be among the compartments having the lowest *AUC* values for the aqueous concentrations of the compounds.

9.3. Short-Term Tests

9.3.1. *Mutagenicity*

In *Salmonella* TA98 and TA100 (with or without activation with microsomal mix or light), color obtained from the National Institute of Hygienic Sciences (Japan) showed no mutational activity.(89) Color obtained from a number of other suppliers was also without effect, over a broad dose range, both in these assays(43,90–93) and in fluctuation analyses using TA1538.(94,95) Certified food color and R-3 from Allied Chemical Co. (93% "pure") was also negative for TA98, TA100, TA1537, and TA1538.(96,97) There was one report that the color formulated by Durand and Huguenin in Switzerland is active in TA100 (an activity that disappears with S9 activation), but not in TA98, TA1535, and TA1538.(98) In *E. coli*, although there is some evidence of an effect in reversion of the pro locus,(99) in WP2 strain there is no effect either in the trp locus(89,90) or when using a fluctuation analysis.(94,95)

In eukaryotes, *S. cerevisiae* D7 and XV185-14C (a haploid) strains showed a significant effect in one locus with a dose response.(100) However, there was no significant induction of *S. chevalieri* respiratory-deficient mutants over a wide dose range using erthyrosine from two different suppliers. In fact, there was an inhibition of mutation induced by 4-nitroquinoline-1-oxide.(101) Gene conversion did not occur in BZ 34 strain, either in resting or log phase under conditions of the test (4-h exposure at 5mg/ml).(102) Gene conversion did occur in the D7 yeast strain over a wide range of doses after a 24-h exposure (100), although there was no effect on intergenic mitotic recombination in D5 strain in the same experiment. There was no effect in inducing lethal *Drosophila* mutations or in onion root tip under conditions of light or dark, although there appeared to be an effect in *Vicia faba* in the light.(36)

Thus, there appears to be little evidence for a mutagenic effect of the color in bacteria or in higher organisms except yeast and *Vicia faba*. Interpretation of the one report of an effect in TA100 is complicated by the lack of response in other, similar strains over a wide range of doses in the same experiment and may be a result of impurities in the particular sample or some experimental factor. In yeast, only some strains appear to be sensitive. The reasons for the differential sensitivity may be related to the different endpoints evaluated and the length of exposure to the agent. Also, the authors suggest that the longer growth period used in the D5 mitotic recombination assay may have selected against the expression of a genetic effect resulting from a short exposure time(99); however, there is little support for this contention. The results in *Vicia faba* may be induced by chemical toxicity since R-3 is phototoxic.(54)

9.3.2. *DNA Damage/Repair*

Although originally found to be negative in a rec assay,(51) which involves damage repairable by a particular enzyme system, the color was later found to give a positive response if the cultures were exposed to light.(89,103,104) R-3 from another source, prepared to commercial standards, gave a negative response(95) with or without light exposure or microsomal activation at a lower dose. In leucocyte cultures exposed to light, there was an inhibition of DNA synthesis.(105) In yeast, the results in D7 showing gene conversion, which may be related to a recombination repair, are difficult to evaluate, as indicated above, especially with the negative results in strain D5. Using hepatocytes, over a wide dose range *in vitro* and at a high dose *in vivo*, the color did not induce any DNA repair.(82)

There appears to be an effect of light and source on the action of this color in solution of inducing DNA damage. The effect of source may be related to the presence of impurities in different formulations. This would be consistent with the results seen in light since storage of the solution in liquid phase for some time by the manufacturer could result in generating active species. The results in these assays should be approached with caution for extrapolation to other biological endpoints. 10^{-4}M is the LC_{50} for human skin cell lines(54) and fetal rat hepatocytes,(104) with the toxic effect in culture suggested to be related to the consequences of dehalogenation.(54)

9.3.3. Chromosomal Damage

In vitro there was no increase in chromosomal aberrations in human lymphocytes(105) (although there was a decrease in DNA synthesis) nor mitotic crossing-over in D5 yeast.(100) There was an increase in chromatid alterations in Ehrlich ascites cells(56) at doses toxic to human cells (although the authors considered the changes mutagenic, there was no evidence the changes were heritable). Positive results in the micronucleus test were reported as evidence of a clastogenic effect in male Swiss mice(107); however, no significant effect was seen in an experiment with better controls in Balb/C mice.(92)

Again the question of toxicity complicates interpretation, especially for unusual tests. Dying cells release compounds which have complex effects on surrounding cells. It is not clear that the chromosomal effects on cells are a result of direct action on the genome.

9.3.4. Transformation

In a transformation assay in Fischer rat embryo cells, no effect was seen.(108)

9.3.5. Significance

In sum, it appears that R-3 is not mutagenic in bacteria, except possibly in a single *E. coli* strain, or in higher organisms, except in some strains of yeast or in *Vicia faba*. The mutagenesis is clearly shown for haploid yeast, and is weak compared to ethyl methanesulfonate. From these results, it also appears that any effect is more related to DNA transitions rather than frameshift mutations. The color is positive in the rec assay after light activation and it affects DNA synthesis. There are chromosomal effects in Ehrlich tumor cells and *Vicia faba*, but not in human lymphocytes. The results in the micronucleus tests, as a whole, show no consistent effect.

The significance of the short-term tests for prediction of long-term toxicity is not straightforward. Except for one test done before modern standardization, the bacterial results for mutation are negative, with toxicity appearing to be a major factor in the positive response in the recombination assays. In yeast, only some strains and endpoints are positive.(109) The haploid reversion mutation assay appears to have an accuracy of approximately 0.6 in predicting carcinogenicity.(110) The yeast mutation assays are not conducted according to an agreed-upon protocol and tend to be redundant to the *Salmonella* test, while the conversion assays are not sufficiently consistent and reproducible between laboratories.(111) The Ehrlich tumor cell assay is hard to interpret because of the instability of the tumor genome. The *Vicia faba*(112) assays require much more development to be predictive of long-term health effects.

The short-term test results for R-3 were evaluated using a recent approach,(113) which predict a probability of carcinogenicity for the color of 0.12 to 1.7%, a value similar to that of sucrose.(114) The results suggest that the color is almost assuredly not a carcinogen acting directly on the genome.

The question of how the toxic effects of the compound, especially the phototoxic effect and the release of iodine, are involved in some of the short-term effects seen is a critical, unanswered one. The effect of toxicity in the assays for genetic damage should be clearly separated from a direct effect on the genome, which is difficult to do for many of these observations since the exposures which are effective seem to be toxic ones.

9.4. Comparative Toxicology

9.4.1. Negative Studies

Rat: R-3 was given at 4% of the diet to a total of 10 male and female Wistar rats for 2 years. One case of hepatic cirrhosis was noted.(60)

R-3 was given at 0.5, 1.0, 2.0, or 5.0% of the diet to groups of 12 male and 12 female Osborne-Mendel rats for 2 years. Growth depression was noted in rats on the 5% level. Spleen weights were decreased. No neoplasms were attributed to the treatment.(115)

Subcutaneous injections of R-3 solutions (total dose = 12 mg/rat) in 9 male and 9 female rats yielded no tumors at the injection site after 2 years.(115)

R-3 was given at 0.1, 0.5, and 1% of the diet to groups of 70 male and 70 female Charles River rats in a two-generation study which lasted for 24 months. No oncogenic effect was noted.(116)

R-3 was given at 0.25, 1, and 4% of the diet to groups of 25 male and 25 female CD rats (at each level) in a three-generation study. There were decreases in body weights of some of the treated groups (4% level). No compound-related effects were noted in the F_{3b} generation.(117)

Mouse: R-3 was given at 0.3, 1, and 3% of the diet for 24 months to 60 male and 60 female Charles River CD mice in each group. Body weights were decreased slightly at the 3% level. No oncogenic effect was noted.(118)

Gerbil: R-3 was fed to groups of 15 or 16 Mongolian gerbils at 1, 2, or 4% of the diet for 105 weeks. In addition, groups of 20–26 male and female gerbils were intubated twice weekly with 200, 750, or 900 mg/kg of R-3 by stomach tube for 97 weeks. Enlargement of the thyroids occurred in animals on the 1–4% dietary levels but neoplasms were not noted.(119)

Dog: R-3 was fed to groups of 3 male and 3 female beagle dogs at 0.5, 1.0, or 2% of the diet for 2 years. No effects due to ingestion of the color additive were seen.(115)

Skin Painting Study: In 50 male and 50 female ICR Swiss-Webster mice, 0.1 ml of a 1% solution of R-3 was painted on skin twice weekly for 18 months. No oncogenic effect was noted.(67)

9.4.2. *Positive Study*

Rat: R-3 was given at 4% of the diet for 24 months to 60 male and 60 female (F_0) and 70 male and 70 female (F_1) CD rats which had been exposed *in utero*. Body weights of treated rats were lower than those of controls. Thyroid weights were increased in treated F_1 males, and the incidence of thyroid follicular tumors was increased.(120)

9.4.3. *Interpretation of Positive Rat Study*

Toxicology. At the highest dietary dose level (4%), R-3 caused moderate body weight gain depression as compared with controls. There was no effect on mortality. Toxic lesions were seen in the thyroid glands of male F_1 rats which appeared to represent a goitrogenic effect of R-3 on the thyroid gland. These doses led to increased thyroid weights in males.

Pathology. Thyroid tumors (follicular adenoma or carcinoma) were found in 18/70 4% males and in only 1/70 control males. Only 3 of 18 rats with thyroid follicular cell tumors had a carcinoma of these cells.

Conclusion. Although R-3 at 4% of the diet with *in utero* exposure induced some weight depression, only a relatively low incidence of induced thyroid tumors was seen. Thyroid toxic lesions were also relatively mild and mortality was not affected. The study does show that R-3 is a goitrogen and thyroid carcinogen in rats.

R-3 was obtained from CTFA as FDA certified lot no. AA 2459 (733 Erythrosin), with a stated color content of 90% (dark red powder). No data were provided in the bioassay report on the presence of impurities or subsidiary colors that may have been present. FDA certification analyses of this lot show 90% color, 3.6% volatile matter, 7% inorganic salts, 0.19% sodium iodide, 0.07% insoluble matter, and nondetectable levels of phthalic acid, 2-(2′,4′-dihydroxy-3′,5′-diiodobenzoyl)benzoic acid and ether extractables. Analyses of subsidiary colors showed 4.66% 2,4,5-triiodofluorescein, 0.33% 2,4,7-triiodofluorescein, 0.2% "x", and 94.8% R-3.(26) The dosing in the study seemed to be well-controlled.

The purity of the color dosed is not stated in definitive terms. All that is shown is that the color was an FDA certified lot of "90% purity." No impurities were reported, however, the FDA certification analyses showed that the principal impurity was 2,4,5-triiodofluorescein. It is unlikely that significant amounts of identified impurities were present to the extent that the risk assessment would be significantly altered.

9.5. Skin Penetration Studies

The *in vitro* studies(15) used ^{14}C-R-3 obtained from the Pathfinder Laboratories, with a specific activity of 4.53 mCi/mmol. Although the report from Pathfinder assured the radiochemical purity of the labeled color,(121) the data, an HPLC tracing with detection at 254 nm, demonstrated only that the material synthesized was, indeed, R-3. These data were totally inadequate to determine whether the radioactive label was actually incorporated in the material termed R-3. There is the possibility of uncolored ^{14}C-labeled starting materials. In light of this, the skin penetration studies are impossible to interpret since it is not certain that the radiolabeled material that penetrated the skin was R-3. There are also concerns about the low counting efficiencies reported, and the lack of skin coloration in the presence of significant ^{14}C, as the author of the study stated when interviewed.(122)

Therefore, there is no adequate study of skin penetration of the color.

9.6. Specific Assumptions Used in the CTFA R-3 Risk Assessment

- *Assumption 1:* For aqueous or ethanol/water solutions, and oil/water emulsions, the absorption rate is 1%, and for talc 0.002% (i.e., the R-19 data) of the applied amount of color, except for those products that need adjustment.

Validity: Unknown and simple and easy to test. Since there is no adequate study available to evaluate this assumption, use was made of the data available for R-19, another xanthene, water-soluble color, as a model for R-3.

Option: Either: (a) Conduct *in vivo* tests for extended periods of time; or (b) Repeat the *in vitro* study with live-skin chambers and for extended periods of time with identified material.

Impact: As a larger molecule, it is unlikely that R-3 penetrates the skin as well as R-19; therefore, the absorption estimation based on R-19 probably overestimates the exposure. The Panel used the R-19 penetrance data.

- *Assumption 2:* 50% of the amount of lipstick applied will be swallowed.

Validity: Unknown but testable.

Option: Conduct a study in women on the amount of lipstick swallowed using a radiochemically labeled color or other tracer. Include measurement of the amount lost due to contact of the lips with other surfaces or to wiping off.

Impact: The Panel agrees with CTFA that 50% is likely to be an overestimation. Since specific data for adjusting the percentage swallowed are not available, the Panel used CTFA's estimate. However, CTFA's estimate of 14.5 mg lipstick per application × 2.86 applications per day × 1% concentration × 50% swallowed results in 3.9 μg/kg-day; not in 5.5 μg/kg-day as stated in the risk assessment.(5)

9.7. Risk Characterization

9.7.1. CTFA Risk Estimates

From data for thyroid follicular tumors in male Charles River CD rats: The data were combined for the two IRDC studies. Due to an interim sacrifice at one year, and since no thyroid tumors were observed before one year, the number of animals at risk was taken to be the number of survivors at one year.

9.7.2. Panel Risk Estimates

Information on the usage frequency of products containing R-3 indicates that five product categories belong to products with an assumed 1% absorption per day, three categories are talc-based products, and two are bath products. Application of the above two groups of product- and color-specific assumptions to these in the CTFA risk assessment report(5) results in a total absorbed amount of color per person per day of:

0.88 μg/day = 0.0166 μg/kg-day as an average of the prospective survey;
0.9016 μg/day = 0.017 μg/kg-day as the upper 90th percentile of the prospective survey;

Table IV. Comparison of Risk Estimates for R-3

	Risk(CTFA/90)[a]	Risk(CTFA/Avg)	Risk/90[b]	Risk/Rea[c]
External	3.2×10^{-8}	1.9×10^{-8}	2.0×10^{-9}	2.0×10^{-9}
Ingested	8.1×10^{-7}	NR[d]	4.9×10^{-7}	0.1×10^{-8}

[a] Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

[b] Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

[c] Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.

[d] NR-Not reported.

The comparable CTFA's estimates were 6.650 and 11.3 μg/day, respectively. In lip products, the daily absorbed dose is 0.20 mg/day or 3.9 μg/kg-day for the 90th percentile. The average dose, according to a survey of lipstick ingestion, is 0.038 mg/day. Appropriate factors of 0.8 and 6/7 were used to adjust for the effect of the general assumptions.

9.7.3. Comparison

The major exposure differences between the CTFA (see Table IV) and Panel estimates derive from exposure from talc products, which is much less when a lower absorption is assumed. For this color, unlike R-19, O-17, and R-9, there was no adequate study of skin penetrance, so the absorption of R-19, a color in the same chemical class, was used. Since this color is a larger molecule, this model probably overestimates penetrance.

9.8. Summary

The color purity of 90% by FDA certification in the long-term assays does not adequately define the nature of the total color content. The amounts of organic impurities and subsidiary colors are defined by FDA certification methods. The starting materials and subsidiary colors found in the lot of R-3 evaluated were not present in large quantities except for 2,4,5-triiodofluorescein (4.4%) and are generally not suspected of being strong carcinogens. The data supporting a finding of carcinogenicity for the color additive are relatively weak. One could conclude that the presence of impurities or subsidiary colors may not significantly affect risk assessment calculations.

The lack of any information on the radiochemical purity of the color makes the penetrance study uninterpretable. The R-19 penetrance data were used, and this probably leads to an overestimate of exposure through the skin.

Stability studies of the compound "on the shelf" will be helpful for the clearer understanding of the toxic effects of R-3, especially when the phototoxic properties of the color are considered. This, and an adequate skin absorption study using live animals (e.g., pig) or people (using color labeled with nontoxic tracers such as the heavy, nonradioactive isotopes of carbon, nitrogen, etc.) would be helpful in estimating the risk.

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RESPONSES OF FRANK E. YOUNG TO QUESTIONS ASKED BY SENATOR KENNEDY

Question: Dr. Young, thank you for your insightful testimony. On the subject of benefits versus risks of pesticides, it is clear that the greater use of pesticides provides substantial economic benefit to the manufacturers of these chemicals. And we know we can quantify the benefits to farmers in terms of increased crop yields. But how does the FDA or EPA value the benefits of pesticides to consumers? And more importantly, how are the risks of cancer and adverse health effects valued, to allow a comparison of benefits versus risks? Do you have a quantitative formula, or do you make a guess as to the magnitude of benefits from pesticides?

Answer: As you know, FDA monitors pesticide residues in the food supply and enforces the tolerances set by EPA. Our role in this regard does not normally involve an assessment of benefits to the consumer or a valuation of the risks and adverse health effects as weighed against those benefits. Such assessments are part of the EPA approval process and so we must defer to EPA on these matters. I did point out at the hearing that the Surgeon General's Report on Nutrition and Health stresses the importance of consuming large quantities of fresh fruits and vegetables and the potential for lowering the risk of disease from doing so. Pesticides obviously play a significant role in making this kind of diet available to the American people. This conclusion obviously does not involve a quantitative formula or a guess as to the magnitude of the benefits, but I do believe that, in general, the benefits from pesticides to consumers are significant.

Question: In your testimony, you indicated your support for the negligible risk standard that would be established by S. 722. Could you tell us your opinion of the state-of-the-art of risk assessment? Are you confident that the risk assessment methodology utilized by FDA and EPA concerning pesticide residues is valid and reliable?

Answer: Current risk assessment methodology cannot, with reliability or confidence, predict the actual human risk associated with carcinogen exposure. Its value is in placing an upper bound on this risk. This means that we can be reasonably confident that the actual human risk from carcinogen exposure will not exceed the risk estimate -- say 10^{-6}. This is because most of the assumptions we must make knowingly resolve the scientific uncertainties in a way that is more likely to overstate than understate the risk. In this respect such risk assessments are conservative. Therefore, actions taken by individuals within these upper bounds with respect to a particular carcinogen or other potentially harmful chemical can be considered to present a negligible risk..

Despite these uncertainties and the conservatism, the use of risk assessment with a negligible risk standard of 10^{-6} will allow more flexibility and a more scientific basis for decisions than is now available to us under the Delaney clause. The Delaney clause is undesirably inflexible in two ways. First, it does not accommodate scientific progress, like improved analytical methods and our increasing capacity to distinguish between the different potencies of carcinogens.

Second, by increasingly requiring Agency action under conditions where the risks appear to be trivial, it misallocates Agency resources and invites public ridicule and disregard for the food safety laws generally. A negligible risk standard as proposed is no panacea and it can't completely solve these problems, but it will help.

Question: You mentioned your opposition to the use of the one-in-a-million standard in defining negligible risk. But under the current negligible risk standard concerning pesticide residues, American consumers have little confidence that the risk of cancer and other adverse health effects is truly negligible. You also argue that we should revise the Delaney clause that requires a zero tolerance for food and color additives. Do you really believe that we should relax our food safety standards and potentially allow a greater risk of cancer from pesticides and other chemicals?

Answer: No, I do not. I believe that the negligible risk standard should be adopted because, as a practical matter, it would afford as much public health protection as the Delaney Clause, and do so in a more scientifically sensible way.

Question: Currently, FDA and EPA share responsibility over pesticide residues on foods. Dr. Young, should this responsibility be the sole responsibility of either FDA or EPA?

Answer: This is an important question, but reorganization won't necessarily provide a solution. The expertise of both agencies is needed to adequately regulate pesticides. EPA examines the broad issues of the contribution of pesticides to soil and groundwater contamination, whereas FDA focuses on monitoring and enforcing pesticide residues in the food supply. A balance of responsibility between strong agencies that cooperate and work together provides the best way to address this.

RESPONSES OF FRANK E. YOUNG TO QUESTIONS ASKED BY SENATOR HATCH

1. Commissioner Young, what [effect] would modifying the Delaney Clause to allow for the approval of new color additives, food additives, or pesticides that only pose a negligible risk of cancer have on the health of the public?

A. We believe it would have no effect on public health because such modification would, by definition, permit the approval of only those substances that pose no more than a negligible risk. Accordingly, such a revision of the law would preclude use of any substance that could have an adverse public health impact.

2. Commissioner Young, in order to increase public confidence in our food supply, should we establish a uniform standard for determining the safety of our food supply?

A. We believe it is wise to set the highest reasonable standard that can be achieved in any situation. At the same time, we recognize that it is pointless to establish requirements stricter than necessary to protect public health. Any standard should be clear and applied consistently in all situations that are similar.

The current law with respect to pesticides, however, is not completely consistent. For example, pesticides which are applied to or concentrate in processed foods are subject to the Delaney Clause in the law, while pesticides in raw agricultural commodities are not. There needs to be a consistent standard for regulating pesticide residues in both types of products.

3. In setting a standard to use for scientific risk assessment, do you believe the standard should be static or dynamic?

A. Risk assessment may require different types of assumptions or models depending on the data available in a given situation. The approach used may change as scientific knowledge grows. Thus, the only standard that applies in all situations is to use the best quality science in the most reasonable way to ensure that no risk is overlooked. There is no "quantitative standard" to be applied in the risk "assessment" stage.

Once risk has been assessed, the risk must be managed; that is, a decision must be made on whether a risk is acceptable in a given situation. This will vary for different situations but standards must be sufficiently clear, and consistently applied so that government action can be reasonably predicted. Public confidence requires assurance that risk management decisions are not arbitrary or dependent primarily on the person making the decision.

4. Commissioner Young, do you have sufficient authority to ensure that unsafe chemicals will not be used in our food supply? And if not, what other authority does FDA need?

A. The Federal Food, Drug, and Cosmetic Act provides sufficient authority to prevent unsafe substances from being used in foods. In some cases, the formal rulemaking procedures required can tax the resources of the Agency, but that is not a question of authority.

5. Commissioner Young, if you were given the appropriate legal tools to control the use of harmful chemicals in our food supply, what additional resources would the FDA need?

A. FDA, USDA, and EPA are currently meeting with the White House Domestic Policy Council to review the regulation of pesticides in the United States. The enforcement and monitoring policies and activities of the three agencies are being discussed, and a number of considerations are being explored. It may therefore be prudent to defer answering this question until deliberations on these matters have been completed.

However, a current illustration of having legal tools but not the additional resources, is that FDA must carry out the mandates of the Pesticide Monitoring Improvements Act of 1988 (PMIA). Three major provisions are to be implemented: (1) development of a long-range analytical methods research plan; (2) establishment of cooperative agreements with the governments of foreign countries to obtain pesticide usage information; and (3) development of a computerized system to summarize and evaluate FDA pesticide monitoring data. At the time it passed this law, Congress did not provide supplemental resources to implement these provisions or to implement any program initiatives which might evolve. We estimate that full implementation of PMIA and associated activities would require an additional $10 million as follows: $4 million for analytical methods research; $2 million to establish cooperative agreements and implement use of the information provided; and $4 million to develop and maintain the computerized data management system.

6. Can you give us an idea of what it costs to test one sample for inert and active compounds? How much do you think it would cost to implement S. 722 as it is currently drafted? What would it do to the cost of our food?

A. On average, analyzing one sample for pesticide residues costs FDA $325.00. This estimate does not include analysis for inerts, nor for all potential pesticide residues. Many inerts require the use of costly single residue methods; inclusion of inerts in FDA's analytical program would approximately triple the cost per sample to about $1000.

Recently, FDA prepared an estimate of the cost to conduct a statistically-based sampling and analysis program for annual apple shipments in the United States, where analyses would be carried out for all pesticides with established tolerances for apples (see attached). This estimate is $50 million for apples alone, and does not include estimates for the costs of analyzing for inert ingredients, which would add considerably to the overall cost. With regard to the potential impact of implementation of S. 722, FDA does not have the means to evaluate the direct cost to food producers and therefore cannot estimate potential cost increases at the wholesale or retail level.

7. Dr. Young, it seems to me that there are two extremes when it comes to testing food. We could either rely on the statements of the food producers and not test anything, or we could test every shipment. Clearly, there must be some middle ground. How do you think we should determine when and how to test for pesticide residues?

A. The large volume of domestic and imported produce, coupled with the enormous number of potential pesticide-commodity combinations, effectively precludes either the government or producers from testing all shipments for every conceivable residue. Nor can existing data be relied on exclusively to demonstrate the safety of the food supply to the consumer. We believe there is a middle ground, one that relies primarily on monitoring by FDA, but which also includes information from other agencies and the States.

In designing and carrying out its monitoring program, FDA considers a wide variety of factors, including toxicity, chemical characteristics, and risks posed by particular pesticides; commodities that may contain residues of these chemicals; and history of past violations. New toxicologic information, EPA concerns, acute contamination problems, and changes in pesticide usage may also dictate specific monitoring activities. FDA's pesticide surveillance program cannot ensure that every violative shipment is intercepted; rather, it is designed to uncover major pesticide residue trends and problems.

There is a dearth of reliable, comprehensive, and current information for domestic and foreign pesticide usage. For the present, FDA draws on data obtained through its own residue monitoring activities, as well as data compiled by the states. FDA is also working with EPA to develop additional data on domestic pesticide use. To improve monitoring of imported commodities, in 1986, FDA purchased data from the Battelle World Agrochemical Data Bank. FDA is also negotiating with the countries which are the major sources of food imports into the United States, to provide current information about the pesticides used in those countries. Using all of this information, FDA will be better able to target its monitoring to detect residues of those pesticides most likely to have been used on a particular crop in a particular country.

Consensus also needs to be reached on the practical level of nationwide sampling required to obtain the optimum amount of information. Addressing these points would lead to a pesticide residue monitoring program better able to provide information sought by consumers, regulatory officials, and food processors.

The **Chairman**. Fine. We will come back to that.

Just before coming back, I want to welcome Senator Cochran. Dr. Young, do we really know the consumption of different foods for the general population?

Dr. **Young**. Yes, we do. That is very important.

The **Chairman**. But that has not been updated, has it?

Dr. **Young**. We do follow it in two different ways. The first and most reliable is we have 20 years of data of cooking eight different meals in different areas, different age groups to look at. And when we cook those meals and analyze them—recognizing, of course, that we can only look at about 50 percent of the total pesticides. But in looking at that, less than two to three percent of all of the foods have any detectable residues that are significant. We can provide that summary for the record, and I will also provide the summary for the record of our recent analysis of pesticides in 1987 that shows that as well.

[The summaries of Dr. Young follow:]

FOOD AND DRUG ADMINISTRATION PESTICIDE PROGRAM

Residues in Foods - 1987

The U.S. Food and Drug Administration (FDA) has conducted an extensive program to monitor the nation's food supply for pesticide residues since the 1960s. Data compiled from these monitoring efforts have shown that the U.S. population's exposure to pesticide residues is consistently below established safety standards. The results of FDA's pesticide monitoring in Fiscal Year 1987 (October 1, 1986, through September 30, 1987), which are summarized in this report, continue to support this observation.

The Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA), and FDA have joint responsibility in the area of pesticides. EPA registers or approves the use of pesticides and establishes tolerances, if use of a pesticide may lead to residues in food. (A tolerance is the maximum amount of a residue expected in a food when a pesticide chemical is used according to the label directions, provided that the level does not present an unacceptable health risk.) With the exception of meat and poultry, for which USDA is responsible, FDA is charged with enforcing tolerances on food shipped in interstate commerce, and, as part of these activities, determines the incidence and levels of pesticide residues in domestically produced and imported foods.

Potential registrants (generally pesticide producers) seeking approval for use of a pesticide on food must submit extensive residue chemistry data from actual field testing to EPA to support the request for a tolerance. Results from toxicological studies must also be submitted as well as data on the pesticide's environmental fate. EPA evaluates these data, weighing the safety of the residue level of the pesticide; the necessity of an adequate and economical food supply; and the other ways in which the consumer may be affected by the same or related chemicals. This balancing of risks and benefits is the basis on which decisions to register a compound are made. In 1987, there were 320 pesticide chemicals with established food and/or feed tolerances in the United States.

Data from over 25 years of FDA monitoring have shown that above-tolerance residues are rarely found, indicating that pesticide chemicals are generally used according to label directions. These violative residues can result from misuse, unusual weather conditions, or poor agricultural practices. More commonly, however, violations involve commodities that contain small amounts of pesticides for which no tolerance has been set. For example, EPA registers a pesticide and sets a tolerance for its residue in lettuce. If this pesticide is found in cabbage and no tolerance exists, any amount of residue found on the cabbage is illegal (although not necessarily a health risk).

FDA may also establish another type of regulatory limit for those pesticides that no longer have approved agricultural uses, but that, by virtue of their persistence for long periods in the environment, may unavoidably contaminate food. These limits, called action levels, are residue levels at or above which FDA may take legal action to remove foods from the market. For example, food uses for DDT were discontinued in the 1970s; however, DDT residues are sometimes found, albeit at low levels. (In a *Federal Register* notice of February 19, 1988, as a result of a recent court ruling FDA announced that its current action levels are not binding on FDA, industry, or the courts.)

Monitoring Programs

Regulatory Monitoring

In this approach, FDA collects samples from individual lots of both domestically grown and imported foods and analyzes them for pesticide residues. The methods used to analyze these samples are generally capable of determining pesticide residues at levels well below tolerance values. When violative residues are found in domestic samples, FDA can initiate various sanctions such as a seizure or injunction. For import samples, shipments may be detained at the port of entry when illegal residues are found.

When violative import samples are discovered for a particular shipper/country/commodity, the certification requirement may be invoked. While the requirement is in effect, the importer is responsible for having each shipment of the commodity in question analyzed and certified by a private laboratory to be free of violative levels of the one or more specific residues in question. In such instances, a certificate of analysis must accompany the import documents for each shipment subject to certification. FDA reviews the certification reports to ensure the adequacy of the analysis.

Selective surveys are initiated to acquire information on specific pesticides, commodities, or pesticide/commodity/country combinations. Additional information might be needed because of pest control activities in a particular area, a need for more data on a particular commodity or on imports from a single country, new information about a pesticide's toxicity, a change in pesticide usage, a specific request from EPA, or concern over a contamination incident.

Domestic samples are collected as close as possible to the point of production in the food distribution chain, since the prime objective is to monitor fresh food being shipped in interstate commerce for compliance with EPA tolerances. Sampling at an early stage of distribution provides the best opportunity to identify shipments of fresh produce and other foods, e.g., raw cabbage, apples, and wheat, that may contain illegal residues and to effect timely regulatory follow-up if necessary.

Few shipments of imported foods contain residues that exceed EPA tolerances.

Import samples are collected at the point of entry into U.S. commerce. Shipments from Mexico are given special attention because of the large volume of fresh and processed foods that enter the United States from that country. This is especially true during the winter, when much of our fresh produce comes from Mexico.

Whether domestic or import, the samples collected are classified as either "surveillance" or "compliance." Most samples are in the first category, that is, they are collected without suspicion that the particular shipment contains illegal residues. Compliance samples are collected and analyzed as follow-up to the finding of an illegal residue or when other evidence indicates that a residue problem may exist in that shipment.

FDA/State Cooperation. - Coordination with state authorities in the development of cooperative sampling plans and information exchanges results in more effective coverage of the domestic food supply and follow-up to correct apparent emerging residue problems. FDA is also supporting, via contract, a system to compile and summarize data on foods analyzed by states for pesticides (and industrial chemicals). In the system, known as "Foodcontam," results for about 15,000 samples were received in 1987 from 5 states. A similar system called "Feedcon" is in place for animal feed data.

In this report, only food monitoring data from FDA have been included.

International Information. - Imported foods represent an increasing proportion of the U.S. food supply. Over the years, FDA has monitored imported food for pesticide residues and, in general, has found that few food shipments contain residues that exceed EPA tolerances. However, to improve FDA's ability to monitor imported foods, particularly fresh fruits and vegetables, FDA purchased in 1986 the Battelle World Agrochemical Data Bank, a computerized data base containing information on foreign pesticide use. Aided by this information, FDA is better targeting its monitoring toward pesticides more likely to have been used on a particular crop in a particular country.

Total Diet Study

The other major approach to monitoring used by FDA is the Total Diet Study. Also known as the Market Basket Study, this effort is designed to estimate the dietary intakes of pesticide residues by 8 age/sex groups, from infants to senior citizens. (Industrial chemicals, heavy metals, radionuclides, and essential minerals are also measured.) FDA personnel purchase foods from local supermarkets or grocery stores, just as a shopper would do, 4 times per year throughout the United States. Each of the 4 market basket samples is a composite of foods collected in 3 cities in a particular region. The cities of collection are changed each year. Each market basket contains 234 individual food items that have been chosen, based on nationwide dietary surveys, to represent the diet of the U.S. population. The foods are prepared table-ready (peeled, cooked, etc.) and then are analyzed for pesticide residues. The results of these analyses, coupled with data on the amounts of these foods consumed, allow for calculation of the dietary intakes of these residues. This provides an estimate of the actual amount of pesticide residues consumed in foods as they are usually eaten, e.g., scalloped potatoes, coleslaw, apple pie, bread, lasagne.

Results and Discussion

Regulatory Monitoring

The total number of samples collected and analyzed each year has averaged 12,600 for the past 10 years. In 1987, 14,492 samples were analyzed. Imported foods made up more than 50% of the total, reflecting FDA's recently increased emphasis on imports.

Figure 1 presents a summary of the residue results (both domestic and imports) of the 14,492 samples in terms of various food groups. Fresh vegetables accounted for the largest number of foods sampled, followed by fruits and a group consisting of milk, dairy products, and eggs. Overall, no violative residues were found in more than 95% of the samples, and in 57% of the samples, no residue was found.

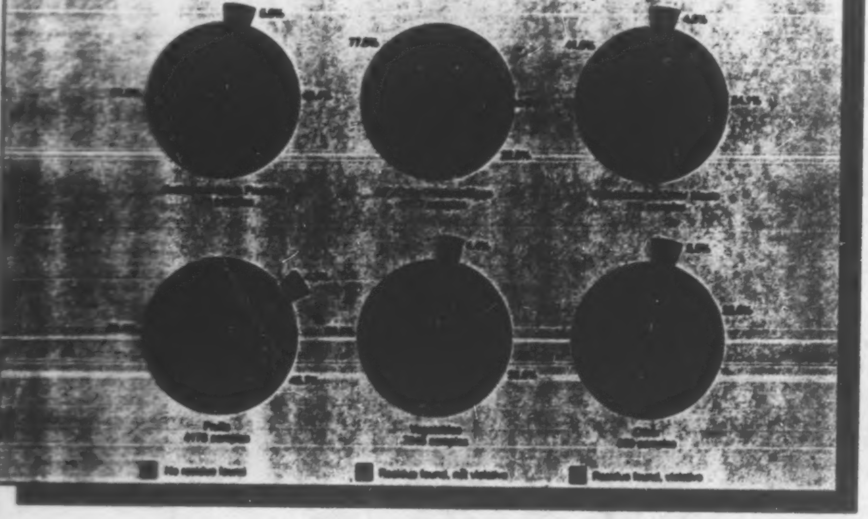
Appendix A provides more detailed data by commodity group for domestic samples. No residues were found in the majority of samples taken of high consumption domestically produced foods. For example, of the more than 3000 fresh vegetable samples analyzed, no residues were found in 63%, less than 1% contained residues over tolerance, and about 2% contained residues for which no tolerance had been established. For fresh fruits, no residues were found in 50%, less than 1% contained over-tolerance residues, and less than 1% contained residues that had no established tolerance. For imports (Appendix B), the picture was substantially the same, but residues of pesticides without tolerances were somewhat more frequent, about 4% for vegetables and 6% for fruits.

No residues were found in 76% of the 847 domestic dairy product samples (milk, cheese, butter, ice cream, etc.), and none contained violative residues. For imported dairy products, 80% of the 270 samples had no detectable residues, no residues were over tolerance, and only 1% contained residues that had no tolerance.

Geographical Coverage - Domestic. - During 1987, domestic samples were collected from the continental United States,

Figure 1

Summary of Results (Domestic and Import) of 1987 Sample Analysis for Pesticide Residues by Commodity Groups



Hawaii, Alaska, and Puerto Rico. Figure 2 illustrates the distribution of the sampling throughout these areas. The largest numbers of samples were collected from those states where agriculture is a major industry. **Import**. - During 1987, samples representing food shipments imported from 79 countries were collected. Figure 3 illustrates the distribution of the sampling by country, and Table 1 lists the number of samples collected and the countries from which they originated. The largest number of samples were collected from Mexico, reflecting the volume and variety of commodities that are imported into the United States from that country. Over time, important foods from additional countries will be sampled.

Pesticide Coverage. - In regulatory monitoring and in the Total Diet Study, foods are analyzed for a wide variety of possible pesticide residues. For some pesticides, several measurable residues of concern, e.g., various isomers, metabolites, or alteration products, may result from the application of one pesticide. In this report, such residues have been combined and are expressed as "total" residues. For example, values for *o,p*′-DDT, *p,p*′-DDT, *o,p*′-DDE, *p,p*′-DDE, *o,p*′-TDE, *p,p*′-TDE, and *p,p*′-TDE olefin have been added and are listed as DDT, total.

Table 2 lists the 253 pesticides that would have been detected if their residues had been present; the 113 pesticides that were found in 1987 are also noted.

Selective Surveys. - A selective survey may determine the occurrence of a particular pesticide or a group of chemically related pesticides in a number of different crops (Table 3) *or* it may focus on sampling of one crop for one or more different pesticides. These surveys are generally aimed at food/pesticide combinations not

Figure 2
Distribution of Sample Collection in 1987 from the United States and Puerto Rico

■ 100 or more samples
■ 11-99 samples
■ 10 or fewer samples

Table 1
Foreign Countries and Number of Samples Collected and Analyzed in 1987

Country	No. of Samples
Mexico	4173
Chile	430
Dominican Republic	412
New Zealand	386
The Netherlands	327
Canada	269
Italy	186
Guatemala	136
Thailand	121
Spain	119
China, Rep. of	92
Belgium	89
Costa Rica	82
France	82
Australia	78
China, People's Rep. of	65
Brazil	63
Ecuador	55
Germany, Fed. Rep. of	47
Hong Kong	45
Greece	44
Argentina	42
Honduras	42
Israel	34
Korea, Rep. of	33
Jamaica	29
Colombia	28
Panama	27
Philippines	27
Turkey	27
India	26
Japan	26
Denmark	25
Haiti	25
United Kingdom	24
Switzerland	23
Austria	21
Norway	19
El Salvador	15
Peru	15
Venezuela	15
Finland	13
Portugal	12
Singapore	12
Netherlands Antilles	11
Yugoslavia	11
Unspecified	35

Ten or fewer samples collected from the following:

Albania
Bahamas
British Virgin Islands
Cambodia
Cyprus
Egypt
Germany, Berlin
Germany, Dem. Rep. of
Guyana
Hungary
Iceland
Indonesia
Iran
Ireland
Ivory Coast
Jordan
Lebanon
Malawi
Malaysia
Morocco
Nigeria
Oman
Pakistan
Poland
Romania
Sri Lanka
Swaziland
Sweden
Tanzania
Trinidad & Tobago
Uganda
Uruguay
Western Samoa

Figure 3
Distribution of Import Sample Collection in 1987

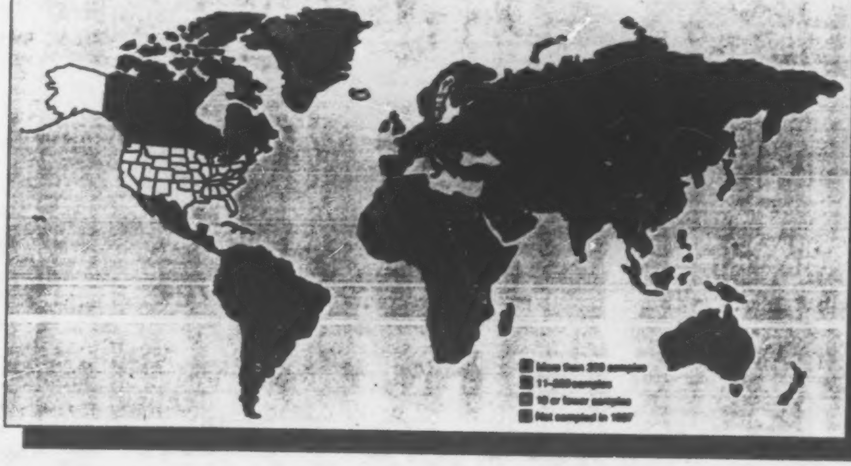


Table 2
Pesticides that Could Have Been Detected or Were Found in 1987 Regulatory Monitoring

Acephate*
Alachlor
Aldicarb*
Aldoxycarb
Aldrin*
Allethrin
Ametryne
Amitraz
Amobam*
Anilazine*
Aramite
Aspon
Atrazine
Azinphos-ethyl
Azinphos-methyl*
Bendiocarb
Benfluralin
Benomyl*
Bensulide
BHC*
Binapacryl
Biphenyl*
Bromacil
Bromophos
Bromophos-ethyl*
Bromopropylate*
Bufencarb
Bulan
Butralin
Captafol*
Captan*
Carbanolate
Carbaryl*
Carbofuran*
Carbon disulfide
Carbon tetrachloride*
Carbophenothion*
Carboxin
Chlorbenside*
Chlordane, total*
Chlordecone
Chlordimeform
Chlorfenvinphos, total*
[illegible]
[illegible]
Chlorobenzilate*
Chloroform*
Chloroneb
Chloropicrin
Chloropropylate
Chlorothalonil*

Chlorpropham*
Chlorpyrifos*
Chlorpyrifos-methyl*
Chlorthion
Chlorthiophos
Command
Coumaphos
Crotoxyphos
Cyanazine
Cycloate
Cyhexatin*
Cypermethrin*
2, 4-D*
2, 4-DB
Daminozide*
DCPA*
DDT, total*
DEF*
Deltamethrin
Demeton
Dialifor
Diallate
Diazinon*
Dibromochloropropane
Dicapthon
Dichlobenil
Dichlofenthion*
Dichlofluanid*
Dichlone
1,3-Dichloropropene
Dichlorvos*
Diclofop-methyl
Dicloran*
Dicofol, total*
Dicrotophos*
Dieldrin*
Diflubenzuron*
Dilan
Dimethoate*
[illegible]
Dinocap*
Dioxacarb
Dioxathion
Diphenamid
Diphenylamine*
Disulfoton, total
Endosulfan, total*
Endrin*
EPN*
EPTC*
Ethion*
Ethoprop*

Ethoxyquin
Ethylene dibromide*
Ethylene dichloride
Ethylene oxide
Etrimfos
Famphur
Fenamiphos
Fenarimol
Fenbutatin oxide*
Fenitrothion*
Fenthion*
Fensulfothion
Fenvalerate*
Fluchloralin
Flucythrinate
Fluvalinate
Folpet*
Fonofos
Gardona*
Genite 923
Heptachlor*
Hexachlorobenzene*
Hydrogen cyanide*
Imazalil*
Iprodione*
Isobenzan
Isodrin
Isofenphos
Isoprocarb
Isopropalin
Jodfenphos
Leptophos
Lindane*
Linuron
Malathion*
Mancozeb*
Maneb*
Mecarbam*
Mephosfolan
Merphos
Metalaxyl
[illegible]
Methamidophos*
Methidathion*
Methiocarb*
Methomyl*
Methoxychlor, total*
Methyl bromide
Methyl trithion
Methylene chloride
Metiram*
Metolachlor

Metribuzin
Mevinphos, total*
Mirex*
Mobam
Monocrotophos*
Nabam*
Naled
Napropamide
Nicotine*
Nitralin
Nitrofen
Norea
Norflurazon
Omethoate*
Ovex*
Oxadiazon
Oxamyl
Oxydemeton-methyl
Oxyfluorfen
Oxytetracycline*
Oxythioquinox
Parathion*
Parathion-methyl*
Pendimethalin
Pentachlorophenol*
Permethrin, total*
Perthane
Petroleum oils
Phencapton
Phenthoate
Phenylphenol, ortho-
Phorate*
Phosalone*
Phosmet*
Phosphamidon
Phoxim
[illegible]
Picloram
Piperalin
Pirimiphos-ethyl
Pirimiphos-methyl*
Procymidone*
Profenofos*
Profluralin
Prolan
Promecarb
Prometryn
Pronamide*
Propanil
Propargite*
Propazine
Propham

Propoxur
Prothiofos
Pyrazon
Pyrazophos*
Pyrethrins
Pyrethroids, synthetic*
Quinalphos*
Quintozene*
Ronnel*
Salithion*
Schradan
Simazine
Strobane
Sulfallate
Sulfotep
Sulfur dioxide*
Sulprofos
2, 4, 5-T
2, 3, 6-TBA
TDE, total*
Tecnazene*
TEPP
Terbacil
Terbufos*
Terbuthylazine
Terbutryn*
Tetrachlorvinphos
Tetrasul
Thiabendazole*
[illegible]
Thionazin
Thiophanate-methyl*
Tolylfluanid*
Toxaphene*
Triadimefon*
Triadimenol
Triallate
Triazophos
Trichlorfon
Trichloronat
Trifluralin
Trimethacarb
Vernolate
Vinclozolin*
Zineb*
Zytron

* = pesticides that were found

normally covered as part of ongoing monitoring.

An example of the first type of selective survey was that carried out in 1987 for EBDCs (ethylenebisdithiocarbamates, a group of fungicides). Sixty-one samples, representing 10 different foods, were analyzed. No EBDC residues were found in 28 of the samples; 30 samples contained EBDC residues that were within legal limits. Three spinach samples, all from the same grower, contained violative EBDC residues. The grower was advised of FDA's findings, and, as a result, voluntarily destroyed 25 cases of harvested spinach and the unharvested spinach in 2 fields.

An example of the second type of selective survey was that carried out on bananas. Eighty-eight banana samples, representing 5 countries, were analyzed. One or more residues were found in 40 samples. Residues of 5 different pesticides were found, all at legal levels, that is, the residues were lower than the tolerance levels.

Certification. - Table 4 lists commodities from specific ship-

Table 3
Selective Surveys Conducted in 1987

Pesticide	Commodity
Aldicarb	potatoes
Benomyl and/or thiophanate-methyl	apples grapes peaches
[illegible]	[illegible]

pers/countries that were subject to the certification requirement in 1987. (This is also known as automatic detention.) Commodities that required certification from all shippers in a country represent situations where an illegal residue was found to be widespread on that commodity within that country. Use of the certification requirement demonstrates the shifting of responsibility for correcting pesticide residue problems to the regulated industry. (In an April 11, 1988, issuance of its Regulatory Procedures Manual, FDA adopted a procedure whereby automatic detention may be invoked when *one* shipment contains actionable levels of a pesticide residue.)

Surveillance/Compliance Violation Rate Comparison. - Only 1.5% of the domestic and 3.4% of the import surveillance samples were violative (Figure 4). These rates would probably be even lower if the surveillance samples were collected in a completely random fashion. However, surveillance samples are chosen partly on the basis of volume of production of a commodity, and also on the basis of prior residue problems with a particular food. Therefore, surveillance sampling is somewhat biased and is not completely objective.

As expected, a higher percentage of the domestic and import compliance samples were violative, 12.1 and 11.6%, respectively (Figure 5). These findings were anticipated because one of the chief purposes of compliance sampling is to define and control problems identified by analysis of surveillance samples.

Figure 4
Domestic and Import Surveillance Sample Violation Rates for 1987

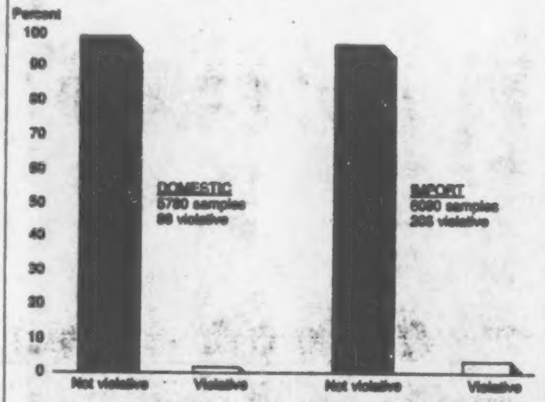


Table 4
Certifications Invoked in 1987

Country	Commodity	No. of Shippers	No. of Pesticides
Australia	apples	1	1
Canada	peppers	1	1
Costa Rica	chayotes	1	1
Dominican Republic	bitter melons	1	1
	eggplant	8	4
	long beans	3	1
	okra	3	2
	peppers	5	3
	snow peas	4	3
	squash	7	3
Guatemala	broccoli	1	1
Mexico	coriander	all	11
	cucumbers	1	1
	grapes	all	1
	okra	3	4
	peppers	2	2
	strawberries	10	2
New Zealand	currants	1	1
Spain	lemons	11	2
Various countries	mangoes	all	1

Figure 5
Domestic and Import Compliance Sample Violation Rates for 1987

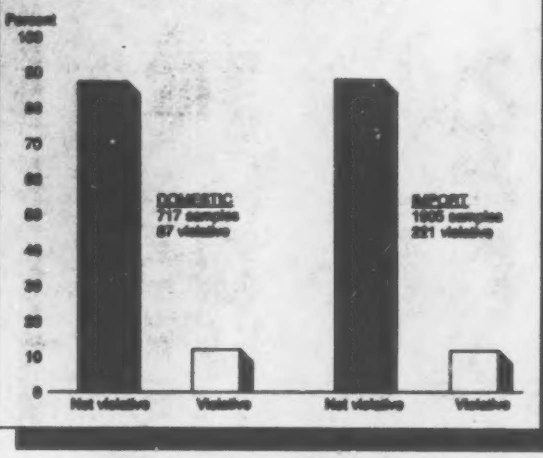


Table 5
Frequency of Occurrence of Pesticides in Total Diet Study in 1987

Pesticide	Total No. of Findings[a]	Percent Occurrence	Pesticide	Total No. of Findings[a]	Percent Occurrence
Malathion	211	23	Acephate	24	3
DDT, total	202	22	Dicofol, total	24	3
Diazinon	194	21	DCPA	20	2
Chlorpyrifos	117	12	Ethion	20	2
Dieldrin	108	12	Dimethoate	19	2
Hexachlorobenzene	91	10	Phosalone	19	2
Endosulfan, total	64	7	Parathion	18	2
BHC, alpha & beta	59	6	Toxaphene	17	2
Lindane	58	6	Permethrin	13	1
Heptachlor	57	6	Omethoate	12	1
Chlordane, total	47	5			
Methamidophos	46	5			
Chlorpyrifos-methyl	44	5			
Dicloran	41	4			
Carbaryl[b]	35	4			
Quintozene, total	32	3			
Chlorpropham	30	3			

[a] Based on 936 items.

[b] Reflects overall incidence; however, only 72 selected foods were analyzed for *N*-methyl carbamates.

Summary: Regulatory Monitoring

In summary, no residues were found in over 50% of all samples (domestic and import) (Figure 6) analyzed under regulatory monitoring in 1987. Of those samples with violative residues, 81% of the violations occurred because there was no tolerance for that specific commodity/pesticide combination. Of the total number of samples, less than 1% had residue levels that exceeded tolerances. These data illustrate that pesticide chemicals are rarely used in a manner that results in residue levels that exceed tolerances.

No residues were found in over half the foods sampled in 1987, and less than 1% contained residues that exceeded tolerances.

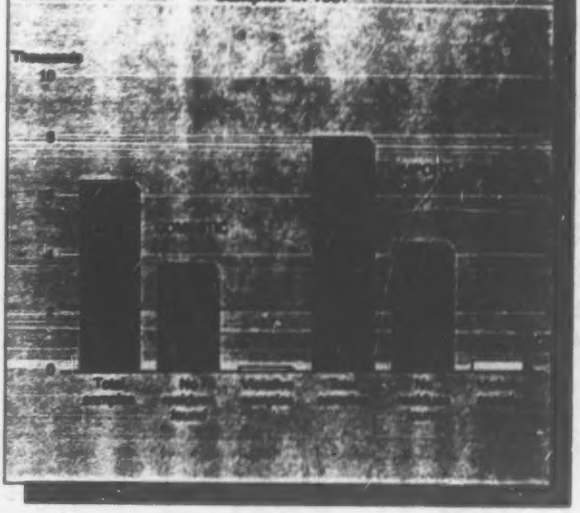
Total Diet Study

While information from regulatory monitoring indicates that the consumer is not exposed to excessive levels of pesticide residues, the Total Diet Study provides a *direct* estimate of dietary pesticide intake. In the Total Diet Study, 234 different food items representing the diets of U.S. consumers are collected and analyzed 4 times each year, resulting in a total of 936 samples analyzed. Of the over 200 chemicals that can be determined by the analytical procedures used, 53 pesticides were found in the 1987 market basket foods. The 27 pesticides most frequently found are listed in Table 5, together with the total number of findings and the percent incidence of occurrence in the 936 samples.

While the analytical methods used in the Total Diet Study are capable of determining only about half the pesticides with U.S. food tolerances, there is no compelling reason to believe that the situation regarding residue levels and corresponding intakes would be any different for those not detectable. This is supported by the results of the selective surveys conducted as part of regulatory monitoring, where it is evident that even when residues are found, the levels are generally small fractions of the tolerance.

ADI Comparisons. - The principal objective of the Total Diet Study is to develop dietary intake information on pesticides and to compare these intakes with acceptable daily intakes (ADIs). An ADI is the daily intake of a chemical which, if ingested over a lifetime, appears to be without appreciable risk. ADIs are established by the United Nations' Food and Agriculture Organization (FAO) and the World Health Organization (WHO). Appendix C lists selected pesticide intakes for 3 of the 8 U.S. population groups covered in the Total Diet Study and the ADIs for those pesticides. The comparisons show that the dietary intakes of pesticide residues are consistently below established ADIs, in most cases by orders of magnitude. For almost all pesticides, the dietary intake is less than 1% of the ADI. These data confirm the wide difference between actual intakes and estimated safe intake levels.

Figure 6
Comparison of Results for Domestic and Import Samples in 1987



Residues on Raw vs Processed Foods. - Total Diet Study analyses focus on table-ready foods rather than on raw, unwashed agricultural commodities. Food preparation often reduces the levels of pesticide residues; therefore, the analytical procedures used in the Total Diet Study are modified to permit measurement at levels one-fifth to one-tenth of those achieved in regulatory monitoring for enforcement of regulatory limits. Were this not the case, far fewer residues would be detected. The amount of a pesticide residue found in Total Diet foods is residue-, commodity-, and preparation-dependent, but, in general, is less than that found in the corresponding raw commodity.

Summary: Total Diet Study

In summary, the results of the Total Diet Study for 1987 demonstrate the very low levels of or undetectable pesticide residues in food as consumed. The data also show that dietary pesticide intakes are manyfold lower than their ADIs. These findings corroborate the continuing safety of the U.S. food supply with respect to pesticide residues.

Total Diet Study results show that dietary pesticide intakes are manyfold lower than safety levels established by WHO.

Summary

A total of 14,492 samples of domestically produced and imported food from 79 countries were analyzed for pesticide residues in 1987. No residues were found in over 50% of the samples. When residues were found, they were usually at low levels and rarely exceeded tolerances. Most violative residues were found in commodities where a tolerance had not been established for a specific pesticide/commodity combination. Less than 1% of the 14,492 samples contained residues that exceeded regulatory limits. These findings are supported by the Total Diet Study data, which show that the dietary intake of pesticide residues is only a small fraction of acceptable limits.

The program described in this report continues with modifications designed to place additional emphasis on imports, better target both domestic and imported foods, increase the number of selective surveys to add information on residue occurrence, and expand FDA/state cooperative activities.

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Appendix A

Analysis of Domestic Samples by Commodity Group in 1987

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative	
			Over Tol.	No Tol.
A. Grains and Grain Products				
Bakery and cereal products/ snack foods	16	31	0	6
Corn, popcorn	72	49	4	0
Grain products	22	59	0	0
Other whole grains	10	20	0	0
Rice	63	46	6[a]	8
Soybeans	19	68	0	0
Wheat	123	29	7	0
Total	325	41	5[a]	2
B. Milk/Dairy Products/Eggs				
Butter/butter products	15	33	0	0
Cheese/cheese products	97	66	0	0
Eggs	302	91	0	0
Ice cream/ice cream products	14	43	0	0
Milk & cream	419	71	0	0
Total	847	76	0	0
C. Fish/Seafoods/Other Meats				
Fish & shellfish	499	27	5[a]	<1
Other meats	4	50	0	0
Total	503	27	5[a]	<1
D. Fruits				
Blackberries	3	67	0	0
Blueberries	21	57	0	0
Boysenberries	5	100	0	0
Cranberries	20	0	0	0
Grapes	127	72	0	0
Raspberries	12	83	0	0
Strawberries	305	18	2	<1
Other berries	13	85	0	0
Grapefruit	14	29	0	0
Oranges	62	24	0	0
Other citrus fruit	12	17	0	0
Apples	243	42	0	0
Pears	69	51	0	0
Other core fruits/mixed fruits	8	12	0	0
Apricots	18	61	0	0
Cherries	84	61	0	0
Nectarines	15	67	0	0
Olives	32	94	0	0
Peaches	100	49	2	0
Plums and prunes	23	83	0	0
Other pit fruits	5	100	0	0
Papaya	26	100	0	0
Pineapples	19	100	0	0
Other tropical fruits	5	100	0	0
Cantaloupe	51	61	0	0
Honeydew	22	68	0	0
Watermelon	70	91	0	1
Other vine fruits	21	67	0	0
Other fruits	11	55	0	36
Fruit jams & toppings	9	33	0	0
Fruit juices	14	86	0	0
Fruits, dried or paste	19	37	0	0
Total	1458	50	<1	<1
E. Vegetables				
Bean sprouts	15	100	0	0
Blackeyed peas	3	33	0	0
Corn	78	92	0	0
Garden/green/sweet peas	55	85	0	0
String beans	59	71	0	3
Other beans, peas, & corn	38	82	3	0
Cucumbers	62	66	0	0
Eggplant	28	68	0	4
Okra	4	75	0	25

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative	
			Over Tol.	No Tol.
Peppers	98	64	0	0
Pumpkins	5	20	0	20
Squash	109	71	0	3
Tomatoes	260	83	0	3
Artichokes	30	63	0	0
Asparagus	56	100	0	0
Bamboo sprouts	2	0	0	0
Broccoli	159	83	0	0
Broccoli raab	10	80	0	0
Brussels sprouts	9	100	0	0
Cabbage	114	82	0	0
Cauliflower	107	96	0	0
Celery	87	18	0	0
Chinese cabbage	27	63	0	22
Collards	41	44	0	7
Dandelion greens	10	30	0	20
Endive/chicory	30	70	0	3
Kale	44	36	0	20
Lettuce	494	34	2	2
Mustard greens	44	39	2	11
Parsley	25	36	0	20
Spinach	82	35	5*	7
Swiss chard	15	73	0	7
Turnip greens	35	23	14	3
Other leaf/stem vegetables	59	63	0	8
Mixed vegetables	2	100	0	0
Mushroom/truffle products	20	90	0	0
Carrots	107	61	<1	0
Leeks	5	100	0	0
Onions	77	75	0	5
Parsnips	20	30	20	0
Potatoes	281	62	0	0
Radishes	30	87	0	0
Red beets	30	77	0	7
Rutabagas	9	67	0	0
Sugar beets	15	93	0	0
Sweet potatoes	55	69	0	0
Turnips	28	61	0	0
Other root/tuber vegetables	16	94	0	0
Vegetable juice	5	100	0	0
Vegetables with sauce	66	70	0	0
Other vegetable-related products	20	65	0	0
Total	3080	63	<1*	2
F Other				
Spices and flavorings	29	62	0	24
Peanuts	27	44	0	0
Pecans	19	100	0	0
Walnuts	19	79	0	0
Sunflower seeds	18	78	0	6
Other nuts, seeds, & related products	12	100	0	0
Refined vegetable oil	16	62	0	0
Vegetable oil seed stock	23	65	0	0
Other vegetable oil products	9	56	0	0
Alcoholic beverages	25	48	0	0
Bottled spring or mineral water	11	100	0	0
Other waters and soft drinks	10	100	0	0
Chocolate & cocoa products	3	100	0	0
Food sweeteners	8	25	0	12
Other food products	61	43	0	0
Total	290	63	0	3
A-F Total	**6503**	**58**	**1***	**1**

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* Includes samples that have both residue(s) over tolerance and residue(s) with no tolerance

Appendix B

Analysis of Import Samples by Commodity Group in 1987

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative Over Tol.	Percent Samples Violative No Tol.
A Grains and Grain Products				
Bakery and cereal products/ snack foods	44	77	0	0
Corn, popcorn	1	100	0	0
Grain products	31	68	0	3
Other whole grains	6	33	0	17
Pasta products	45	76	0	9
Rice	20	85	0	0
Wheat	6	67	0	0
Total	153	74	0	4
B Milk/Dairy Products/Eggs				
Butter/butter products	1	100	0	0
Cheese/cheese products	230	85	0	1
Eggs & egg products	34	50	0	3
Milk & cream	1	0	0	0
Filled & imitation milk	4	100	0	0
Total	270	80	0	1
C Fish/Seafoods/Other Meats				
Fish & shellfish	197	78	0	<1
Other meats	15	20	0	47
Total	212	74	0	4
D Fruits				
Blackberries	15	53	0	0
Blueberries	31	77	0	0
Boysenberries	7	29	0	0
Cranberries	4	25	0	0
Grapes	451	30	0	13
Raspberries	65	38	0	3
Strawberries	329	40	0	12
Other berries	40	10	0	12
Grapefruit	10	80	0	0
Lemons	57	23	0	32
Limes	27	93	0	0
Oranges	43	37	0	0
Tangerines	29	45	0	0
Other citrus fruits	9	78	0	22
Apples	161	51	0	1
Pears	110	41	0	2
Other core fruits/mixed fruits	9	78	0	0
Apricots	14	36	0	0
Cherries	7	43	0	0
Nectarines	24	42	0	0
Olives	9	100	0	0
Peaches	58	41	0	0
Plums and prunes	21	43	0	0
Other pit fruits	15	87	0	0
Bananas	154	68	0	0
Mangoes	41	63	0	22
Papaya	15	93	0	7
Pineapples	75	85	0	1
Plantains	17	94	0	0
Other tropical fruits	92	87	0	0
Cantaloupe	266	39	<1	6
Honeydew	108	33	<1	2
Watermelon	154	69	0	<1
Bitter melons	59	81	0	3
Other vine fruits	20	60	0	0
Other fruits	15	33	0	7
Fruit jams & toppings	17	82	0	0
Fruit juices	55	89	0	0
Fruits, dried or paste	87	85	0	0
Total	2720	51	<1	6
E Vegetables				
Blackeyed peas	83	69	0	16
Corn	28	100	0	0
Garden/green/sweet peas	170	62	<1	4

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative	
			Over Tol.	No Tol.
Mung beans	17	59	0	0
String beans	145	59	0	<1
Other beans, peas, & corn	130	65	0	28
Cucumbers	224	38	2	1
Eggplant	199	43	0	9
Okra	148	75	0	8
Peppers	825	38	2	7
Pumpkins	5	80	0	0
Squash	454	64	<1	2
Tomatoes	721	35	<1	<1
Other fruits used as vegetables	31	74	0	3
Artichokes	10	90	0	0
Asparagus	76	96	0	1
Bamboo sprouts	10	100	0	0
Broccoli	110	60	0	<1
Broccoli raab	9	89	0	0
Brussels sprouts	57	63	2	0
Cabbage	23	91	0	0
Cauliflower	30	87	0	0
Celery	19	11	0	5
Chinese cabbage	9	89	0	0
Endive/chicory	113	78	0	6
Kale	5	60	0	0
Lettuce	31	48	3	6
Parsley	4	75	0	25
Spinach	15	33	0	0
Other leaf/stem vegetables	56	71	0	16
Mixed vegetables	8	63	0	0
Mushroom/truffle products	38	84	3	5
Carrots	32	59	0	0
Leeks	5	100	0	0
Onions	88	76	0	0
Potatoes	27	93	0	4
Radishes	42	90	0	0
Red beets	2	100	0	0
Shallots	23	100	0	0
Sweet potatoes	5	80	0	20
Turnips	4	75	0	0
Other root/tuber vegetables	72	92	0	0
Vegetable juice	7	71	0	0
Vegetables, dried or paste	106	76	8	0
Vegetables with sauce	37	62	0	0
Other vegetable-related products	12	75	0	0
Total	4265	55	<1	4
F. Other				
Whole coriander	97	68	0	19
Whole fennel	20	50	0	0
Other whole spices	35	66	0	11
Ground spices	10	60	0	0
Other spices and flavorings	17	59	0	6
Peanuts	13	31	0	0
Other nuts & related products	28	96	0	4
Sesame seeds	11	100	0	0
Other seeds & related products	12	75	0	0
Refined vegetable oil	4	75	0	0
Other vegetable oil products	6	50	0	33
Alcoholic beverages	3	100	0	0
Beverage bases	13	85	0	0
Coffee & tea	52	85	0	2
Bottled spring or mineral water	7	86	0	0
Other waters and soft drinks	2	100	0	0
Chocolate & cocoa products	11	91	0	0
Food sweeteners	14	93	0	0
Other food products	14	57	0	0
Total	369	73	0	7
A-F Total	**7969**	**56**	**<1**	**5**

Appendix C

Pesticide Intakes (μg/kg body wt/day) Found in Total Diet Analyses and Their ADIs for 3 Age/Sex Groups in 1987

Pesticide	FAO/WHO ADI[a]	Age/Sex Group		
		6-11 mo.	14-16 yr M[b]	60-65 yr F[b]
Acephate	3	0.0025	0.0031	0.0047
Aldoxycarb	5[c]	0.0002	0.0001	0.0002
BHC, alpha + beta	—[d]	0.0019	0.0017	0.0007
BHC, gamma (lindane)	10	0.0010	0.0018	0.0007
Captan	100	0.0194	0.0088	0.0244
Carbaryl	10	0.1550	0.0173	0.0227
Carbofuran, total	10[c]	0.0001	0.0001	0.0001
Chlordane, total	0.5[c]	0.0015	0.0018	0.0015
Chlorobenzilate	20	0.0090	0.0031	0.0026
Chlorothalonil	3(T)[e]	<0.0001	<0.0001	0.0001
Chlorpropham, total	—	0.1432	0.2072	0.1189
Chlorpyrifos	10	0.0207	0.0065	0.0040
Chlorpyrifos-methyl	10	0.0054	0.0066	0.0036
2, 4-D	300	<0.0001	<0.0001	0.0001
DCPA	—	0.0015	0.0011	0.0019
DDT, total	20[c]	0.0348	0.0191	0.0104
Diazinon	2	0.0146	0.0123	0.0066
Dicloran	30	0.2767	0.0682	0.1793
Dicofol, total	25	0.0329	0.0103	0.0101
Dieldrin	0.1[c]	0.0101	0.0045	0.0040
Dimethoate	10	0.0092	0.0009	0.0024
Endosulfan, total	8[c](T)	0.0724	0.0206	0.0400
Endrin	0.2	<0.0001	<0.0001	0.0001
Ethion	6(T)	0.0168	0.0063	0.0070
Fenitrothion	3	0.0004	0.0005	0.0005
Folpet	10(T)	0.0078	0.0029	0.0096
Fonofos	—	<0.0001	<0.0001	<0.0001
Gardona	—	0.0002	<0.0001	0.0001
Heptachlor, total	0.5[c]	0.0030	0.0018	0.0009
Hexachlorobenzene	—	0.0026	0.0018	0.0010
Iprodione	300	0.0064	0.0025	0.0038
Linuron	—	0.0010	0.0003	0.0004
Malathion	20	0.1395	0.1193	0.0710
Methamidophos	0.6	0.0092	0.0087	0.0215
Methiocarb	1[c]	—[f]	0.0004	0.0030
Methomyl	10(T)	0.0022	0.0029	0.0033
Methoxychlor, *p,p'*	100	0.0007	0.0005	0.0003
Mevinphos, total	1.5[c]	0.0126	0.0046	0.0139
Monocrotophos	0.6	<0.0001	<0.0001	<0.0001
Omethoate	0.3	0.0025	0.0011	0.0034
Parathion	5	0.0062	0.0007	0.0016
Parathion-methyl	20	0.0001	0.0001	<0.0001
Pentachlorophenol	—	0.0001	0.0002	0.0001
Permethrin, total	50[c]	0.0710	0.0300	0.0405
Perthane	—	0.0042	0.0016	0.0024
Phosalone	6	0.0808	0.0034	0.0040
Phosmet	20[c]	0.0078	0.0021	0.0049
Pirimiphos-methyl	10	0.0012	0.0016	0.0002
Quintozene, total	7[c]	0.0011	0.0011	0.0005
Sulfur	—	0.0025	0.0009	0.0031
Tecnazene	10	—[f]	<0.0001	<0.0001
Toxaphene	—	0.0101	0.0138	0.0099
Vinclozolin	40[c](T)	0.0121	0.0044	0.0145

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[a] ADIs are usually expressed as mg/kg body wt/day but are expressed here as μg/kg body wt/day for ease of comparison. The ADIs cited here reflect revisions made in 1987.

[b] M=male, F=female.

[c] Includes other (related) chemicals.

[d] ADI not established.

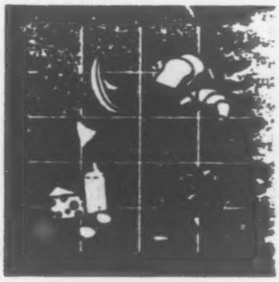
[e] T="temporary" ADI.

[f] No consumption of a food item containing this residue in this age/sex group.

FOOD AND DRUG ADMINISTRATION PESTICIDE PROGRAM

RESIDUES IN FOODS-1988

This is the second annual report in a series about the Food and Drug Administration's (FDA) pesticide residue monitoring program. The first report, which was published in the November/December 1988 issue of the **Journal of the Association of Official Analytical Chemists,** *described the FDA program and presented the results of monitoring for pesticide residues in the U.S. food supply for Fiscal Year (FY) 1987 (October 1, 1986, through September 30, 1987). The present paper explains the changes made in the FDA program since 1987, reports the results of FDA's pesticide monitoring for FY88 (October 1, 1987, through September 30, 1988), and compares some of the FY88 findings with those of FY87.*



The Environmental Protection Agency (EPA) registers or approves the use of pesticides and, if use of a pesticide may result in residues in foods, establishes tolerances. (A tolerance is the maximum amount of a residue expected in a food when a pesticide is used according to the label directions, provided that the level does not present an unacceptable health risk.) FDA is responsible for enforcing tolerances on food shipped in interstate commerce (except for meat and poultry, for which the U.S. Department of Agriculture is responsible), and, as part of its activities, determines the incidence and levels of various pesticides in domestically produced and imported foods. About 300 pesticide chemicals have food and/or feed tolerances in the United States.

FDA's monitoring of the food supply for over 25 years has shown that above-tolerance residues are rarely found. Violations more commonly involve commodities that contain small amounts of pesticides for which no tolerance has been set.

Residues of some pesticides that are no longer approved for agricultural use are unavoidably present at very low levels in both domestic and imported foods due to their persistence as environmental contaminants. In such situations, FDA establishes action levels, based on EPA recommendations, for enforcement purposes. These action levels specify the level below which FDA may exercise its discretion not to take enforcement action. FDA issued a notice in the February 19, 1988, *Federal Register* which stated that its action levels are not binding on the courts, the public (including food producers), or the agency (including individual FDA employees). Thus, if a food (or feed) contains a pesticide residue below the action level for that substance, FDA, through the Department of Justice, is not precluded from initiating seizure, injunction, or prosecution. At the same time, if a food contains a pesticide residue above the action level for that chemical, FDA is not necessarily required to take legal action. Whether legal action is taken in a given case will depend on several factors, such as the extent of the contamination, the strength of the evidence of contamination, and the risk to public health.

MONITORING PROGRAMS

Regulatory Monitoring

To fulfill its mandated responsibilities, FDA collects samples from individual lots of domestically produced and imported foods and analyzes them for pesticide residues. The analytical methods used to measure the residues are generally capable of determining levels well below tolerance values. When violative residues are found in domestic samples, FDA can initiate various sanctions such as a seizure or injunction. For import samples, shipments may be detained at the port of entry when illegal residues are found.

FDA examines raw produce as well as ready-to-eat foods.

Samples, both domestic and import, are classified as either "surveillance" or "compliance." Most samples collected by FDA are in the first category, that is, they are collected without suspicion that a particular shipment contains illegal residues. Compliance samples are collected and analyzed as follow-up to the finding of an illegal residue or when other evidence indicates that a residue problem may exist in that shipment.

When a shipment of an imported food from a particular grower or shipper is found to contain illegal pesticide residues, FDA may invoke automatic detention for future shipments of the food from that same source. While automatic detention is in effect, the importer is responsible for having each shipment of the commodity in question analyzed and certified by a private laboratory (most of them are in the United States) to be free of violative levels of the specific residue(s) in question.

Prior to 1988, the automatic detention of foods due to illegal pesticide residues was known as the certification requirement. In 1988, FDA revised the criteria for imposing automatic detention. Now, automatic detention may be invoked based on the finding of *one* violative sample if the product contains violative levels of a pesticide residue and there is reason to believe that the same situation will exist in future lots during the same shipping season for a specific shipper, grower, geographic area, or country.

For fresh produce, automatic detention remains in effect for all subsequent lots of the same produce for the rest of the growing season unless the grower/shipper demonstrates that the residue problem no longer exists or that the produce to be shipped originated in fields that were not treated with the pesticide in question.

FDA/State Cooperation.—Local or regional FDA personnel may interact with state departments of food and agriculture, health departments, plant boards, milk boards, or other similarly named divisions within a state's governmental organization. The types and amount of interaction between FDA and individual states vary, but nearly all states (except those few for whom agriculture is a minor concern and who therefore have a limited formal pesticide program) have some cooperative effort. A number of states meet regularly with FDA personnel to share information, discuss mutual problems, and, in some cases, to coordinate state/FDA sampling plans. About half of the states currently supply residue data to their FDA regional counterparts, and some exchange residue data with FDA at set intervals. Several states emphasize testing of milk/dairy products, grains, or seafoods if those commodities are of major economic interest, and this allows FDA to concentrate its efforts on other commodities. Instances of violative samples are immediately brought to the attention of the other party, and if FDA determines that a lot is violative, the state may assist by embargoing the violative shipment.

Six states (California, Florida, Massachusetts, New York, Virginia, and Wisconsin) presently contribute their monitoring data to "Foodcontam," a system supported by FDA via contract (with Mississippi State University) to compile state data on pesticide residues in foods. In 1988, data reflecting several thousand samples were received from these states. The overall findings are reviewed and considered by individual FDA Districts in the development of pesticide monitoring plans and to uncover potential problem areas.

This report, as in 1987, covers only FDA food monitoring data.

International Information.—Import commodities continue to represent an increasing proportion of the U.S. food supply. The Battelle World Agrochemical Data Bank, a computerized data base containing information on use of pesticides in foreign countries, has been used by FDA since 1986 to assist in the planning of FDA's monitoring of imported produce. In addition, the Pesticide Monitoring Improvements Act of 1988 requires that FDA enter into cooperative agreements with the governments of countries that are major sources of imported foods or whose imports into the United States may be important in terms of their volume, dietary significance, or potential pesticide problems.

Priority will be placed on obtaining information on pesticide usage from those countries that are not covered by existing data sources such as the Battelle data base. Countries will be asked to provide information identifying the pesticides used in the production, transportation, and storage of food products imported into the United States. If available, information on regional or local pesticide use, the individuals and agencies responsible for the registration and monitoring of the use of pesticides, the laboratories used by the country's government, and any documents that describe approved pesticide uses, application rates, and residue levels will be obtained. FDA has initiated negotiations with representatives of the various countries.

Total Diet Study

The Total Diet Study, also known as the Market Basket Study, is the other major approach used by FDA to monitor pesticide residues in the food supply. The Total Diet Study is designed to estimate the dietary intakes of pesticide residues (as well as industrial chemicals, toxic elements, and essential minerals) by 8 age/sex groups, from infants to senior citizens. Foods are purchased from local supermarkets or grocery stores by FDA personnel 4 (or sometimes 5) times per year throughout the United States. Each of the 4 market baskets represents a different geographic region and is a composite of foods collected in 3 cities in the particular region. The cities are changed each year. Each market basket contains 234 food items that have been chosen, based on nationwide dietary surveys, to represent the diet of the U.S. population. The foods are prepared table-ready—ranging from peeling bananas to making beef and vegetable stew—and then are analyzed for pesticide residues. These results, in combination with food consumption data, allow for calculation of the dietary intakes. This provides an estimate of the actual amount of pesticide residues consumed by the U.S. population.

RESULTS AND DISCUSSION

Regulatory Monitoring

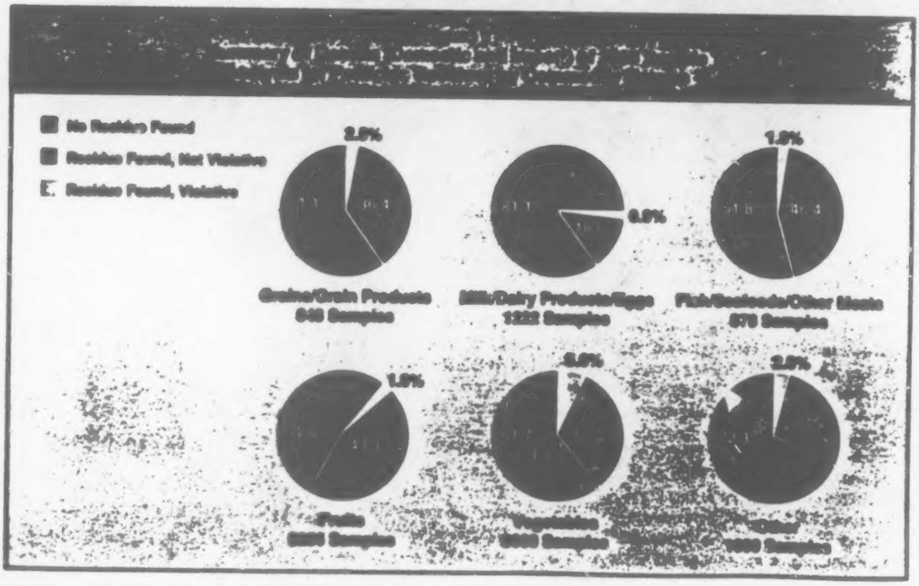
In 1988, 18,114 samples were analyzed through the regulatory monitoring approach, an increase of 25% over the total number of samples analyzed in 1987, reflecting a small increase in allocation of resources. Domestic and import sampling increased 17 and 31%, respectively, in 1988. Imported foods made up more than 57% of the total number of samples (55% in 1987), reflecting FDA's continuing emphasis on imports.

Imports comprised over half of the total number of samples analyzed; foods from 89 countries were sampled.

Figure 1 presents a summary of the residue findings (both domestic and import) for the 18,114 samples in terms of various commodity groups. More samples were analyzed in 1988 in every one of the food groups. As in 1987, fresh vegetables accounted for the largest number of foods sampled, followed by fruits and the milk/dairy products/eggs group. Overall, no violative residues were found in more than 96% of the samples, and in 61% of the samples, no residues were found. In 1987, no residues were found in 57% of the samples.

The lower limit of residue measurement in FDA's analysis for a given pesticide is well below the tolerance level. In general, residues present at 0.01 part per million (ppm) and above are measurable; however, for individual pesticides, this limit may vary from about 0.005 to 1 ppm. FDA attempts to maintain uniform application of the analytical methods in all of its laboratories.

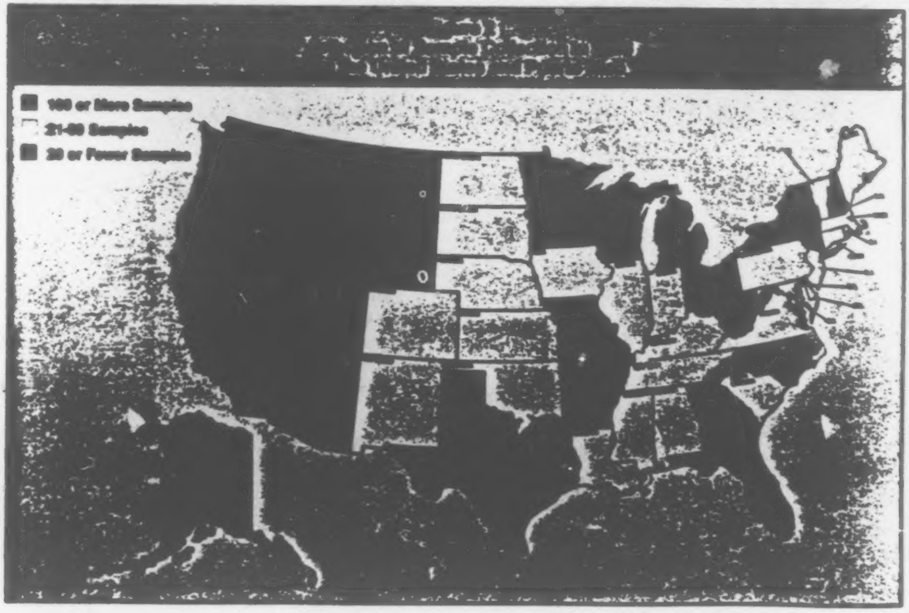
Appendix A provides more detailed data by commodity group for domestic samples including the total number of samples analyzed, the percent samples with no residues found, and the percent violative samples. Of

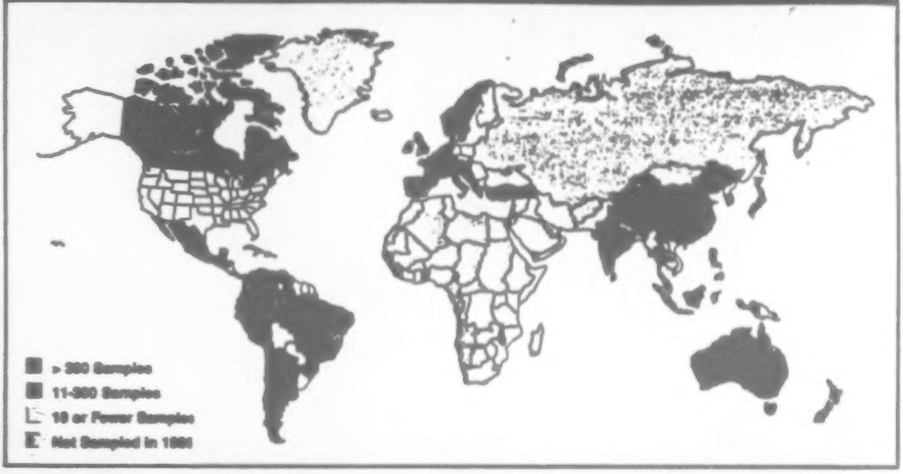


the 7639 domestic samples analyzed, 60% had no detectable residues, less than 1% had over-tolerance residues, and 1% had residues of pesticides for which there are no tolerances for the particular pesticide/commodity combination. No residues were found in the majority of samples reflecting foods of major dietary importance. For example, of the more than 3400 fresh vegetable samples analyzed, no residues were found in 65%, less than 1% contained residues over tolerance, and 2% contained residues for which no tolerance had been established. For fresh fruits, no residues were found in 49%, less than 1% contained over-tolerance residues, and less than 1% contained residues that had no established tolerance. No residues were found in 81% of the 946 domestic dairy product samples (milk, cheese, butter, etc.), and less than 1% contained violative residues.

Appendix B shows the findings for imported foods. Of the 10,475 import samples analyzed, 62% had no detectable residues, less than 1% had over-tolerance residues, and 5% had residues of pesticides for which there are no tolerances for the particular pesticide/commodity combination. Samples with residues of pesticides without tolerances were 6% for vegetables and 2% for fruits. Less than 1% of the fruit samples and less than 1% of the vegetable samples contained over-tolerance levels of residues. Included in the 3171 imported fruit samples that were analyzed were 133 samples of bananas and 27 samples of plantains (Appendix B). Of these, 81% of the bananas and 96% of the plantains had no detectable residues. No violative residues were found in any of these samples. In 1987, of 154 bananas and 17 plantains analyzed, 68 and 94%, respectively, had no detectable residues, and no samples were violative. For imported dairy products, 82% of the 276 samples had no detectable residues, no residues were over tolerance, and 2% contained residues that had no tolerance.

Geographical Coverage—Domestic.—During 1988, domestic samples were collected from all 50 states and Puerto Rico. Figure 2 shows the distribution of the sampling throughout the nation. The largest numbers of samples were collected from states where agriculture is a major industry. **Import.**—Samples representing food shipments imported from 89 countries





Country	No. of Samples	Country	No. of Samples	Country	No. of Samples
Mexico	4395	India	62	Norway	11
Dominican Republic	901	Turkey	58	Switzerland	11
Chile	636	Brazil	54	Unspecified	26
Canada	601	Denmark	52		
New Zealand	382	United Kingdom	52		
Italy	326	Australia	51		
The Netherlands	304	Colombia	45		
Spain	274	Germany, Fed. Rep. of	38		
Thailand	255	Malaysia	32		
Guatemala	234	Haiti	30		
China, Rep. of	213	El Salvador	27		
China, People's Rep. of	132	Portugal	27		
Costa Rica	104	Panama	25		
Greece	101	Trinidad & Tobago	24		
Jamaica	101	Venezuela	22		
Belgium	96	Indonesia	21		
Honduras	86	Yugoslavia	21		
Argentina	81	Hungary	19		
France	78	Peru	18		
Israel	76	Lebanon	17		
Ecuador	74	Austria	15		
Korea, Rep. of	73	Sweden	14		
Philippines	70	Malawi	13		
Japan	69	Singapore	12		
Hong Kong	62	Fiji Islands	11		

Ten or fewer samples collected from the following:

Bahamas
Belize
Bolivia
Bulgaria
Cambodia
Cyprus
Czechoslovakia
Egypt
Finland
French Polynesia
Germany, Dem. Rep. of
Ghana
Grenada
Guadeloupe
Iceland
Iran
Iraq
Ireland
Ivory Coast
Kenya
Macao
Morocco
Mozambique
Nigeria
Pakistan
Poland
Rumania
Saudi Arabia
Sierra Leone
Spanish Sahara
Sri Lanka
Sudan
Tunisia
Uganda
Uruguay
Western Samoa
Zaire

[illegible]

Acephate*
Alachlor
Aldicarb*
Aldoxycarb*
Aldrin*
Allethrin
Ametryn
Amitraz
Amobam*
Anilazine*
Aramite
Aspon
Atrazine
Azinphos-ethyl
Azinphos-methyl*
Bendiocarb
Benfluralin
Benomyl*
Bensulide
BHC*
Binapacryl
Biphenyl
Bromacil
Bromophos
Bromophos-ethyl
Bromopropylate*
Bufencarb
Bulan
Butralin
Captafol*
Captan*
Carbaryl*
Carbendazim*
Carbofuran*
Carbon disulfide
Carbon tetrachloride*
Carbophenothion*
Carboxin*
Chlorbenside
Chlorbromuron
Chlordane*
Chlordecone
Chlordimeform
Chlorfenvinphos*
Chlornidine
Chlornitrofen
Chlorobenzilate*
Chloroform*
Chloroneb
Chloropicrin
Chloropropylate
Chlorothalonil*
Chloroxuron
Chlorpropham*
Chlorpyrifos*
Chlorpyrifos-methyl*
Chlorthion
Chlorthiophos
Clofentezine*
Clomazone
Coumaphos
Cyanazine
Cycloate
Cyhexatin*
Cypermethrin*
2,4-D*
2,4-DB
Daminozide*
DCPA*
DDT*
DEF*
Deltamethrin*
Demeton*
Dialifor
Diallate
Diazinon*
Dibromochloropropane
Dicapthon
Dichlobenil*
Dichlofenthion
Dichlofluanid*
Dichlone
Dichlorobenzene, ortho
Dichlorobenzene, para
1,3-Dichloropropene
Dichlorvos*
Diclofop-methyl
Dicloran*
Dicofol*
Dicrotophos*
Dieldrin*
Dilan
Dimethoate*
Dinitramine
Dinocap
Dioxacarb
Dioxathion
Diphenamid
Diphenylamine*
Disulfoton*
Diuron
Endosulfan*
Endrin*
EPN*
EPTC
Ethion*
Ethoprop
Ethoxyquin
Ethylene dibromide*
Ethylene dichloride*
Etrimfos
Famphur
Fenamiphos
Fenarimol
Fenbutatin oxide
Fenitrothion*
Fensulfothion
Fenthion*
Fenvalerate*
Fluchloralin
Flucythrinate
Fluometuron
Fluvalinate
Folpet*
Fonofos*
Gardona
Genite 923
Heptachlor*
Hexachlorobenzene*
Imazalil*
Iprodione*
Isobenzan
Isodrin
Isofenphos
Isoprocarb
Isopropalin
Jodfenphos
Leptophos
Lindane*
Linuron*
Malathion*
Mancozeb*
Maneb*
Mecarbam*
Mephosfolan
Merphos*
Metalaxyl
Metasystox thiol
Methamidophos*
Methidathion*
Methiocarb*
Methomyl*
Methoxychlor*
Methyl bromide
Methyl trithion
Methylene chloride
Metiram*
Metobromuron
Metolachlor
Metribuzin
Mevinphos*
Mirex
Monocrotophos*
Monolinuron
Nabam*
Naled
Napropamide
Nicotine
Nitralin
Nitrofen
Norea
Norflurazon
Omethoate*
Ovex
Oxadiazon
Oxamyl*
Oxydemeton-methyl*
Oxyfluorfen
Oxythioquinox*
Parathion*
Parathion-methyl*
Pendimethalin
Pentachlorophenol*
Permethrin*
Perthane*
Phenkapton
Phenthoate*
Phenylphenol, ortho*
Phorate*
Phosalone*
Phosmet*
Phosphamidon*
Phostex
Phoxim
Picloram
Pirimicarb*
Pirimiphos-ethyl*
Pirimiphos-methyl*
Procymidone*
Profenofos*
Profluralin
Prolan
Prometryn
Pronamide*
Propanil
Propargite*
Propazine
Propham
Propoxur
Prothiofos
Pyrazon
Pyrazophos*
Pyrethrins
Pyrethroids, synthetic*
Quinalphos*
Quintozene*
Ronnel
Salithion
Schradan
Simazine
Strobane
Sulfallate
Sulfotep
Sulfur*
Sulfur dioxide*
Sulprofos
2,4,5-T
2,3,6-TBA
TDE*
Tecnazene*
TEPP
Terbacil
Terbufos
Terbuthylazine
Tetradifon
Tetraiodoethylene
Tetrasul
Thiabendazole*
Thiodicarb
Thionazin
Thiophanate-methyl
Tolylfluanid
Toxaphene*
Triadimefon*
Triadimenol*
Triallate*
Triazophos
Tributyltin*
Trichlorfon*
Trichloronat
Trifluralin*
Trimethacarb
Vernolate
Vinclozolin*
Zineb*
Zytron

Some of these pesticides are no longer manufactured or registered for use in the United States.

* = pesticides that were found.

were collected. This is an increase of 10 countries over 1987, and represents the increasing emphasis on monitoring of imported foods. Figure 3 shows the distribution of the sampling by country, and Table 1 lists the number of samples collected and the countries from which they originated. As in 1987, the largest number of samples were collected from Mexican shipments, reflecting the volume and variety of commodities that are imported into the United States from that country, especially during the winter months.

Pesticide Coverage.—Table 2 lists the 256 pesticides that were detectable in commodities analyzed by the methods applied; the 118 pesticides that were found are also noted; these numbers are similar to those for 1987. As in the 1987 report, individually identified residues of isomers, metabolites, impurities, and alteration products have not been listed separately; only the "parent" pesticides from which they arise are named.

Commodity/Pesticide Residue Occurrence.—Several pesticides have been of particular interest recently, among them aldicarb, benomyl, and daminozide (trade name Alar). FDA's monitoring for these residues in the past few years indicates that, when found, their levels are well below the tolerances set by EPA.

Aldicarb.—In FY86 through FY88, 3737 domestic and import samples were analyzed by methods capable of determining aldicarb and its 2 major metabolites, the sulfoxide and the sulfone ("total aldicarb"). Of these, 3656 samples (98%) contained no detectable residues. Included in the 3737 samples were 312 potato samples (304 domestic and 8 import). No aldicarb residues were found in 82% of the samples. The highest level found was 0.71 ppm; the EPA tolerance on potatoes is 1 ppm. Also included in the 3737 samples were 55 samples of imported bananas. No residues of aldicarb were found in 98% of the banana samples. One sample contained 0.12 ppm total aldicarb (the tolerance is 0.3 ppm). Residues present at about 0.01 ppm and above would have been measured.

Benomyl.—In FY88, 352 samples of various foods (181 domestic and 171 import) were analyzed by methods capable of determining benomyl and related compounds. The samples included bananas; various berries; grapes; citrus, core, and pit fruits; pineapples; and several vegetables. Of the 352 samples, 31 domestic and 71 import samples contained detectable benomyl residues; no violative residues were found. Residues present at about 0.05 ppm and above would have been measured.

Daminozide.—In FY81 through FY88, 657 samples of various domestic and imported foods were analyzed for daminozide and/or UDMH (a daminozide impurity and degradation product). The majority of the samples were apples or apple products (dried, juice, juice concentrate, pomace, or sauce), but also included were canned and frozen sour cherries; cherry preserves; eggs; grapes; grape juice; grape syrup/topping; milk; peaches; peanuts; pears; peppers; squash; and tomatoes. When found, the residues were well below the tolerances for daminozide. Residues in these foods. The highest level of daminozide found in apples was 8.2 ppm. At the time (1981) the tolerance was 30 ppm; the present tolerance is 20 ppm. The tolerances for the other foods that were analyzed range from 0.02 ppm for milk, 0.2 ppm for eggs, and 0.5 ppm for tomatoes to 10–55 ppm for fruits and peanuts. Currently, residues present at about 0.2 ppm and above can be measured.

Selective Surveys.—A selective survey is designed to determine the occurrence of a particular pesticide or a group of chemically related pesticides in several different crops or to focus on a particular commodity or group of commodities. A number of selective surveys initiated by the FDA Center for Food Safety and Applied Nutrition were carried out for individual pesticides in 1988. Examples include surveys for aldicarb, benomyl and/or thiophanate-methyl, carbofuran, daminozide, and linuron. Surveys initiated or under way in 1988 that focused on food commodities included imported fresh and processed fruits and vegetables, foods imported from Africa, and imported processed stone fruits.

Automatic Detention.—Table 3 lists the commodities from specific shippers/countries that were subject to automatic detention in 1988. The list is more than double that for 1987 as a consequence of the new FDA procedure whereby automatic detention may be invoked when only *one* shipment is found to be violative. Requiring certificates of analysis, in effect, increases FDA's monitoring coverage.

[illegible]

Country	Commodity	No. of Shippers	No. of Pesticides
Belgium	corn salad	1	1
	leaf lettuce	1	1
Canada	cucumbers	1	1
	endive	1	1
Chile	asparagus	2	1
	pears	1	1
	raspberries	2	2
China, Rep. of	chinese pea pods	3	2
China, People's Rep. of	peppers	1	1
Colombia	lulos	1	2
Costa Rica	cantaloupe	1	1
	chayotes	1	2
	pumpkins	1	1
Dominican Republic	bitter melons	7	1
	cilantro	1	1
	eggplant	10	4
	green beans	2	1
	long beans	9	2
	okra	8	4
	peppers	9	2
	snow peas	3	5
	squash	15	5
	tamarinds	1	1
France	mushrooms	1	1
Guatemala	cantaloupe	1	1
	papayas	1	1
	snow peas	4	2
	squash	1	1
	sugar peas	1	1
Honduras	cantaloupe	1	1
	snow peas	1	1
Italy	endive	1	1
	grapes	1	1
Jamaica	calaloo	2	3
	peppers	3	3
	yams	1	1
Mexico	chayotes	1	1
	chinese beans	1	1
	coriander	all	5
	green beans	1	1
	kale	1	1
	lettuce	1	1
	peppers	20	7
	pineapples	1	1
	snow peas	1	1
	squash	3	3
	strawberries	2	2
	sugar peas	1	1
	tomatillos	12	4
Panama	honeydew melons	1	1
Spain	clementines	1	2
	lemons	5	2
The Netherlands	mushrooms	1	1
Venezuela	tomatoes	1	1

For simplicity, general commodities (including processed products) are listed rather than specific varieties.

No residues were found in over 60% of the foods sampled, and less than 1% contained residues that exceeded tolerances.

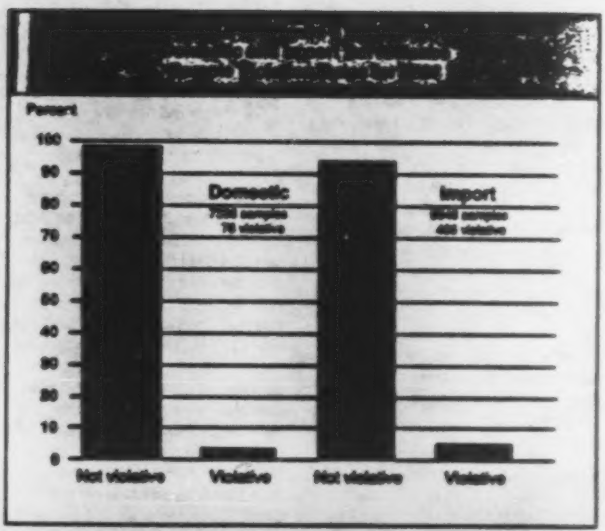
Surveillance/Compliance Violation Rate Comparison.—About 1% of the domestic and 4.2% of the import surveillance samples were violative (Figure 4). Since surveillance sampling is based on a number of factors including usage patterns and volume, commodity treatment history, dietary importance of the commodity, the toxicity of the pesticide, known problem areas, past monitoring results, and knowledge of local usage, the results may be biased toward higher violation rates than if the samples were collected in a truly random or statistical fashion. As expected, a much higher percentage of the compliance samples were violative: 24.9% for domestic and 14.5% for imports.

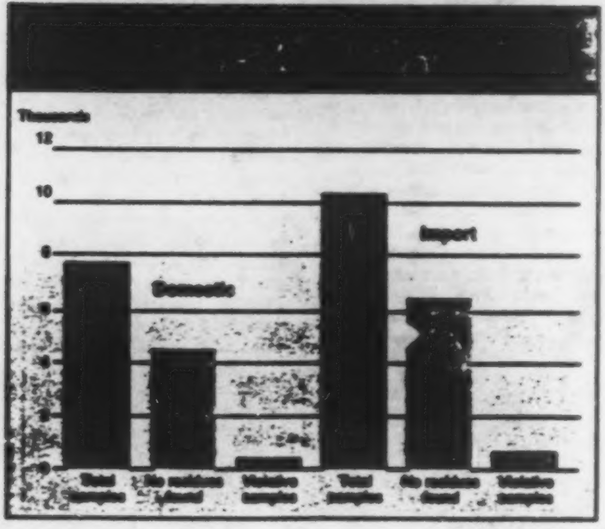
Summary: Regulatory Monitoring

In summary, no residues were found in over 60% of all samples (domestic and import) (Figure 5) analyzed under regulatory monitoring in 1988. Of those samples with violative residues, 84% of the violations occurred because there was no tolerance for that specific pesticide/commodity combination. Of the total number of samples, less than 1% had residue levels that exceeded tolerances. These data corroborate the findings and conclusions presented in the 1987 report, demonstrating again that pesticide residues in foods are generally well below tolerance levels.

Total Diet Study

Regulatory monitoring provides a general overview of the U.S. population's exposure to pesticide residues, whereas the Total Diet Study estimates pesticide residue intake via the diet for several age/sex groups. Analyses for the Total Diet Study are performed on foods prepared for consumption rather than on raw, unwashed commodities collected close to harvest, as is the case for regulatory monitoring. Thus, the Total Diet Study findings, in general, reflect the lower level of residues found in prepared food compared to raw commodities. In the Total Diet Study, 234 different food items representing the diets of U.S. consumers are collected. (In 1988, 5 market baskets were collected, resulting in a total of 1170 items.) Of the more than 200 chemicals that can be determined by the analytical methods used, 55 were found in the 1988 market basket foods. Because many residues dissipate with time and because food preparation may further reduce levels of pesticide residues, the analytical procedures used in the Total Diet Study are designed to permit measurement at levels 5 to 10 times lower than those employed in regulatory monitoring. If these lower levels were not attainable, far fewer residues would be found. Although the level varies with the chemical and food item, in general, residues present at or above about 0.001 ppm are measured. Residues consisting of a mixture of related chemicals generally are not measurable until a higher residue level is reached. The 30 most frequently found pesticides are listed in Table 4, together with the total number of findings and the percent occurrence in the 1170 samples. The 4 most frequently found pesticides were the same in 1988 and 1987.


Percent
100
90
80
70
60
50
40
30
20
10
0
Domestic
samples
violative
Import
samples
violative
Not violative
Violative
Not violative
Violative


Thousands
12
10
8
Domestic
Import
Total samples
No residues found
Violative samples
Total samples
No residues found
Violative samples

Data collected over several years through the Total Diet Study can provide an historical perspective on pesticide residue occurrence in the food supply. For example, in the 6-year period from 1982 to 1988, 72 foods from each of 24 market baskets (1728 food items) were analyzed for aldicarb and its metabolites. Two samples were found to contain these residues: boiled potatoes (0.01 ppm) and fresh/frozen broccoli (0.02 ppm). During this same time, 24 banana samples were analyzed as part of the Total Diet Study. No pesticide residues were found in the edible portion of these samples. In 24 samples of banana and pineapple with tapioca (strained/junior foods), there was only one pesticide residue finding, malathion, at a level of 0.005 ppm.

ADI Comparisons.—The primary purpose of the Total Diet Study is to estimate the dietary intake of pesticides (plus industrial chemicals, toxic elements, radionuclides, and essential minerals) and compare these with acceptable daily intakes (ADIs). An ADI is the daily intake of a chemical which, if ingested over a lifetime, appears to be without appreciable risk. ADIs are established by scientific experts who attend annual joint meetings of the United Nations' Food and Agriculture Organization (FAO) and the World Health Organization (WHO) to evaluate, among other things, the toxicity of pesticides. Appendix C lists the intakes of a number of pesticide residues for 3 of the age/sex groups encompassed by the Total Diet Study and the ADIs for those pesticides. These are representative of the 8 age/sex groups typically covered. As in 1987, the dietary intakes of pesticide residues are below established ADIs. For most of the pesticides, these intakes are less than 1% of the ADI, reaffirming the wide difference between actual intakes in foods as consumed and estimated safe levels.

Summary: Total Diet Study

In summary, the findings of the Total Diet Study for 1988 corroborate the 1987 findings of very low levels of pesticide residues in food as consumed. As in 1987, the data show that pesticide intakes via the diet are generally manyfold lower than their ADIs. (Detailed information on the results of the Total Diet Study has been published in the *Journal of the Association of Official Analytical Chemists*.) The 1988 findings again show the continuing safety of the U.S. food supply relative to pesticide residues.

[illegible]

Pesticide[a]	Total No. of Findings[b]	Percent Occurrence	Pesticide[a]	Total No. of Findings[b]	Percent Occurrence
Malathion	242	21	[illegible]	27	2
DDT	237	20	DCPA	22	2
Diazinon	171	15	Parathion	20	2
Chlorpyrifos	126	11	Omethoate	18	2
Dieldrin	122	10	Phosalone	[illegible]	2
Chlorpyrifos-methyl	115	10	Toxaphene	[illegible]	2
Endosulfan	[illegible]	8	Permethrin	[illegible]	1
Hexachlorobenzene	[illegible]	7	Captan	[illegible]	[illegible]
Dicloran	70	6	[illegible]	[illegible]	[illegible]
Methamidophos	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Heptachlor	[illegible]	[illegible]			
BHC, alpha & beta	[illegible]	[illegible]			
Lindane	[illegible]	[illegible]			
Chlordane	[illegible]	[illegible]			
Chlorpropham	[illegible]	[illegible]			
[illegible]	[illegible]	[illegible]			
[illegible]	[illegible]	[illegible]			
Carbaryl	[illegible]	[illegible]			
[illegible]	[illegible]	[illegible]			
[illegible]	[illegible]	[illegible]			

[a] Isomers, metabolites, and related compounds [illegible]

[b] [illegible]

[c] [illegible]

SUMMARY

A total of 18,114 samples of domestically produced food from all 50 states and Puerto Rico and imported food from 89 countries were analyzed for pesticide residues in 1988. This compares with 14,492 samples in 1987, with imports from 79 countries. No residues were found in over 60% of the samples, compared to 57% in 1987. Less than 1% of the 18,114 samples contained residues that exceeded the tolerances set by EPA. These findings, together with those from the Total Diet Study and the 1987 report, continue to demonstrate that dietary intakes of pesticide residues are well below standards set by FAO/WHO.

FDA pesticide monitoring concerned with imported foods was given increased emphasis in 1988. Automatic detention was invoked based on the finding of *one* violative sample of an imported commodity. A project was begun to obtain pesticide use data directly from a number of foreign countries that export foods to the United States.

This report confirms previous findings of very low levels of pesticide residues in the food supply.

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APPENDIX A

Analysis of Domestic Samples[a] by Commodity Group in 1988

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative: Over Tol.	Percent Samples Violative: No Tol.
A. Grains and Grain Products				
Corn, popcorn	74	47	1	0
Rice	73	82	1	1
Soybeans	42	57	0	0
Wheat	180	33	2	2
Other whole grains	26	42	0	4
Bakery & cereal products/snack foods	5	80	0	0
Rice products	16	100	0	0
Other grain products	18	61	0	0
Total	436	61	1	1
B. Milk/Dairy Products/Eggs				
Butter/butter products	28	61	0	0
Cheese/cheese products	124	73	2	0
Eggs/egg products	299	90	0	1
Milk & cream/milk products	495	79	0	0
Total	946	81	<1	<1
C. Fish/Seafoods				
Fish & shellfish Total	447	36	2	1
D. Fruits				
Blueberries	29	34	0	0
Cranberries	38	0	0	0
Grapes	146	72	0	0
Raspberries	33	73	0	0
Strawberries	287	24	<1[b]	<1
Other berries	34	56	0	0
Grapefruit	37	14	0	0
Oranges	160	37	0	0
Other citrus fruits	71	24	0	0
Apples	392	38	0	0
Pears	70	61	0	0
Other core fruits/stoned fruits	2	0	0	0
Apricots	49	58	20	0
Cherries	101	50	1	0
Nectarines	49	51	0	0
Peaches	177	38	0	0
Plums & prunes	58	72	0	0
Other pit fruits	5	100	0	0
Papaya	22	100	0	0
Pineapples	31	100	0	0
Other tropical fruits	25	80	0	12
Cantaloupe	77	73	0	0
Honeydew	19	58	0	0
Watermelon	96	82	0	0
Other vine fruits	14	64	0	0
Other fruits	18	72	0	22
Fruit jams & toppings	16	56	0	0
Fruit juices	26	100	0	0
Fruits, dried or paste	37	86	0	0
Total	2086	46	<1[b]	<1[b]
E. Vegetables				
Bean sprouts	11	100	0	0
Corn	123	96	0	0
Garden/green/sweet peas	62	82	0	0
String beans	86	79	0	0
Other beans, peas, & corn	30	70	0	10
Cucumbers	105	61	0	16
Eggplant	16	47	0	0
Peppers	86	43	2	0
Squash	76	66	0	1
Tomatoes	335	75	0	<1
Other fruits used as vegetables	6	83	0	0
Artichokes	15	73	0	0
Asparagus	43	86	0	0
Broccoli	127	94	0	0

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative	
			Over Tol.	No Tol.
Brussels sprouts	19	95	0	0
Cabbage	140	90	0	0
Cauliflower	111	95	0	0
Celery	77	40	0	0
Chinese cabbage	64	55	0	31
Collards	36	39	0	8
Endive/chicory	70	61	7[b]	7
Kale	50	50	2	2
Lettuce	663	44	1	<1
Mustard greens	35	31	6[b]	6
Parsley	6	17	0	50
Spinach	116	84	0	3
Swiss chard	7	57	0	0
Turnip greens	37	19	3	3
Other leaf/stem vegetables	43	84	0	0
Mushroom/truffle products	32	44	0	0
Carrots	107	49	0	0
Leeks	11	91	0	0
Onions	99	76	0	1
Parsnips	9	22	0	33
Potatoes	323	71	2	0
Radishes	20	80	0	0
Red beets	15	67	0	0
Rutabagas	8	38	0	0
Sweet potatoes	122	65	0	3
Turnips	15	47	0	0
Other root/tuber vegetables	7	86	0	0
Vegetable juices	11	82	0	0
Vegetables, dried or paste	86	66	0	0
Vegetables with sauce	25	80	0	0
Total	3401	66	<1[a]	2
F. Other				
Spices & flavorings	20	85	0	0
Peanuts	24	85	0	0
Pecans	26	96	0	0
Sunflower seeds	6	100	0	0
Other nuts, seeds, & related products	15	87	0	0
Crude vegetable oil	45	80	0	0
Refined vegetable oil	30	73	0	0
Alcoholic beverages	40	40	0	0
Soft drinks & waters	15	100	0	0
Food sweeteners	23	70	0	22
Other food products	70	80	0	0
Total	334	72	0	2
A-F Total	7636	60	<1[a]	1

[a] Includes both surveillance and compliance samples.

[b] Includes samples that have both residue(s) over tolerance and residue(s) with no tolerance.

APPENDIX B

Analysis of Import Samples[a] by Commodity Group in 1988

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative	
			Over Tol.	No Tol.
A. Grains and Grain Products				
Rice	64	95	0	0
Wheat	10	40	0	0
Other whole grains	11	82	0	0
Bakery & cereal products/snack foods	23	87	0	0
Pasta products	37	68	0	11
Rice products	41	98	0	0
Other grain products	26	58	0	4
Total	212	82	0	2
B. Dairy Products/Eggs				
Cheese/cheese products	210	89	0	0
Eggs/egg products	66	59	0	8
Total	276	82	0	2
C. Fish/Seafoods/Other Meats				
Fish & shellfish	418	77	0	0
Other meats	13	54	0	23
Total	431	77	0	<1
D. Fruits				
Blackberries	26	15	0	19
Blueberries	72	72	0	0
Boysenberries	10	20	0	0
Grapes	365	52	0	<1
Raspberries	105	42	1	3
Strawberries	189	17	0	0
Other berries	46	24	0	4
Grapefruit	12	83	0	0
Lemons	43	47	0	16
Limes	47	94	0	0
Oranges	120	64	0	2
Tangerines	32	22	0	3
Other citrus fruits	11	55	0	27
Apples	94	46	0	1
Pears	71	72	0	6
Mixed fruits	6	100	0	0
Apricots	24	29	0	0
Avocados	10	100	0	0
Cherries	31	39	0	0
Nectarines	47	4	0	0
Olives	124	91	0	2
Peaches	115	49	<1	2
Plums & prunes	53	19	0	0
Other pit fruits	13	92	0	0
Bananas	133	81	0	0
Breadfruit	11	100	0	0
Mangoes	79	99	0	0
Papaya	40	90	0	5
Pineapples	228	70	<1	2
Plantains	27	96	0	0
Other tropical fruits	120	81	0	8
Cantaloupe	309	38	<1	3
Honeydew	104	38	0	1
Watermelon	46	87	0	0
Bitter melons	106	78	0	10
Other vine fruits	34	68	0	3
Other fruits	10	20	0	0
Fruit jams & jellies	69	88	0	0
Fruit juices	81	79	0	0
Fruit toppings	27	93	0	4
Fruits, dried or paste	99	77	0	3
Total	3171	58	<1	2
E. Vegetables				
Blackeyed peas	13	77	0	0
Corn	42	100	0	0
Garbanzo beans/chick peas	23	78	4	0
Garden/green sweet peas	347	48	3	12
Mung beans	15	67	0	13
String beans	295	54	2	10
Other beans, peas, & corn	132	67	0	6
Cucumbers	254	37	<1	2
Eggplant	226	66	<1	4
Okra	189	74	0	9

Commodity Group	Total No. of Samples	Percent Samples with No Residues Found	Percent Samples Violative	
			Over Tol.	No Tol.
Peppers	1051	46	1[b]	7
Pumpkins	20	90	0	5
Squash	658	69	<1	6
Tomatillos	162	37	0	33
Tomatoes	364	45	<1	1
Other fruits used as vegetables	66	71	0	9
Asparagus	96	94	2	0
Bamboo sprouts	11	100	0	0
Broccoli	122	75	0	0
Broccoli raab	31	87	0	0
Brussels sprouts	51	71	0	2
Cabbage	37	89	0	0
Cauliflower	54	89	0	0
Celery	35	26	0	0
Chinese cabbage	36	33	0	25
Collards	14	21	0	0
Endive/chicory	93	77	0	4
Kale	41	15	0	10
Lettuce	143	50	1	2
Mustard greens	14	21	7	0
Parsley	37	16	0	46
Spinach	71	49	4	7
Turnip greens	25	12	16	0
Other leaf/stem vegetables	109	82	0	14
Mixed vegetables	8	50	0	0
Mushroom/truffle products	108	87	0	<1
Carrots	83	58	1	0
Leeks	15	93	0	0
Onions	85	79	0	0
Potatoes	30	77	0	0
Radishes	62	82	0	0
Red beets	27	70	0	0
Shallots	20	80	0	5
Sweet potatoes	21	90	0	0
Turnips	17	88	0	0
Water chestnuts	16	100	0	0
Other root/tuber vegetables	96	96	0	1
Vegetables, dried or paste	180	71	0	6
Vegetables with sauce	45	84	0	0
Other vegetable-related products	7	100	0	0
Total	8679	60	<1[b]	6
F. Other				
Whole coriander	65	83	0	5
Other whole spices	83	81	0	6
Ground spices	21	48	5	5
Other spices & flavorings	11	91	0	0
Cashews	31	77	0	6
Coconuts	14	100	0	0
Other nuts & related products	25	92	0	0
Edible seeds & related products	18	78	0	6
Crude vegetable oil	75	81	0	0
Refined vegetable oil	170	85	0	0
Other vegetable oil products	11	91	0	0
Alcoholic beverages	16	94	0	0
Coffee & tea	45	73	0	2
Waters & nonalcoholic beverages	30	97	0	0
Chocolate & cocoa products	66	57	0	0
Other food products	23	96	0	0
Total	785	73	<1	2
A-F Total	10475	82	<1[b]	6

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[a] Includes both surveillance and compliance samples.

[b] Includes samples that have both residue(s) over tolerance and residue(s) with no tolerance.

APPENDIX C

Pesticide Intakes (µg/kg body wt/day) Found in Total Diet Analyses and Their ADIs for 3 Age/Sex Groups in 1988

Pesticide	FAO/WHO ADI[a]	Age/Sex Group 6-11 mo.	14-16 yr M[b]	60-65 yr F[b]
Acephate	3	0.0106	0.0080	0.0104
Azinphos-methyl	2.5	0.0013	0.0039	0.0031
BHC, alpha + beta	–[c]	0.0006	0.0014	0.0010
BHC, gamma (lindane)	10	0.0008	0.0014	0.0009
Captan	100	0.0296	0.0141	0.0366
Carbaryl	10	0.0519	0.0066	0.0124
Chlordane, total	0.5[d]	0.0007	0.0007	0.0010
Chlorobenzilate	20	0.0056	0.0018	0.0011
Chlorpropham, total	–	0.1639	0.2140	0.0876
Chlorpyrifos	10	0.0141	0.0071	0.0061
Chlorpyrifos-methyl	10	0.0125	0.0175	0.0080
DCPA	–	0.0011	0.0009	0.0013
DDT, total	20[d]	0.0661	0.0264	0.0115
DEF	–	<0.0001	<0.0001	<0.0001
Diazinon	2	0.0067	0.0059	0.0033
Dicloran, total	30	0.1866	0.0364	0.0666
Dicofol, total	25	0.0217	0.0086	0.0156
Dieldrin	0.1[d]	0.0114	0.0049	0.0036
Dimethoate	10[e]	0.0077	0.0020	0.0063
Diphenylamine	20	0.0141	0.0417	0.0330
Endosulfan, total	8[d, e]	0.0376	0.0109	0.0224
Endrin	0.2	<0.0001	<0.0001	0.0001
Ethion	6[e]	0.0119	0.0039	0.0033
Fenitrothion	3	0.0014	0.0023	0.0017
Fenvalerate	20	0.0010	0.0006	0.0010
Folpet	10[e]	0.0009	0.0003	0.0011
Fonofos	–	0.0001	0.0001	<0.0001
Heptachlor, total	0.5[d]	0.0040	0.0017	0.0007
Hexachlorobenzene	–	0.0016	0.0011	0.0006
Iprodione, total	300	0.0017	0.0013	0.0014
Linuron	–	0.0025	0.0009	0.0012
Malathion	20	0.1360	0.1202	0.0619
Methamidophos	0.6	0.0136	0.0133	0.0253
Methidathion	5	0.0010	0.0008	0.0007
Methiocarb	1[e]	0.0001	<0.0001	<0.0001
Methomyl	10[e]	0.0006	0.0011	0.0006
Methoxychlor, p,p'	100	0.0003	0.0001	0.0001
Mevinphos, total	1.5[d]	0.0017	0.0006	0.0080
Monocrotophos	0.6	–[f]	<0.0001	0.0001
Omethoate	0.3	0.0024	0.0026	0.0062
Parathion, total	5	[illegible]	0.0006	0.0015
Parathion-methyl	20	0.0002	0.0001	0.0002
Pentachlorophenol	–	0.0004	0.0002	0.0003
Permethrin, total	50[e]	0.0376	0.0737	0.1075
Perthane	–	0.0003	0.0001	0.0002
Phorate, total	0.2[e]	0.0001	0.0002	0.0002
Phosalone	6	0.1227	0.0007	0.0007
Phosmet	20[e]	0.0111	0.0032	0.0064
Pirimiphos-methyl	10	0.0002	0.0001	0.0001
Quintozene, total	7[e]	0.0006	0.0016	0.0006
Sulfur	–	0.0090	0.0119	0.0126
Tecnazene, total	10	0.0003	0.0002	0.0002
Toxaphene	–	0.0067	0.0079	0.0116
Triallate	–	0.0001	<0.0001	0.0001
Vinclozolin	40[e, d]	0.0071	0.0033	0.0061

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[a] ADIs are usually expressed as mg/kg body wt/day but are expressed here as µg/kg body wt/day for ease of comparison.

The ADIs cited here reflect revisions made in 1987.

[b] M = male, F = female.

[c] ADI not established.

[d] Includes other (related) chemicals.

[e] "Temporary" ADI.

[f] No consumption of a food item containing this residue in this age/sex group.

Dr. YOUNG. I think that one of the problems with the public has been that EPA does not have the ability to take some of these pesticides off the market as rapidly as we would like. There has been a lot of attention on this point, some of which has been magnified and possibly not completely scientifically founded.

The CHAIRMAN. We hope to come back to this as a lot of this obviously does not include foods. But we will come back.

The CHAIRMAN. Mr. Kimm.

Mr. KIMM. I, too, would like to very briefly summarize the prepared testimony and have the full statement included in the record.

The CHAIRMAN. Your full statement will be included in the record.

Mr. KIMM. Thank you.

Basically, EPA has two paramount concerns with the bill as drafted. The first is that it deals with the fact that while the proposed bill would bring the tolerances, the two different types of tolerances we set, under a single rubric, it does not deal with the problem of a different basis: negligible risk for tolerances, if this bill is enacted, as opposed to the FIFRA registration which looks at the other benefits associated with the use of the pesticide.

Second, we are particularly concerned that with a number of aspects of the bill as drafted it ends up being too rigid and inflexible to give us the kind of operating discretion that we need to best serve the public interest and provide the maximum amount of public health protection by being able to shift as our perception of risks changes over time.

To begin with, 722 as you indicated in your statement includes a number of elements that we think significantly improve the process. It certainly sets a single standard for tolerances. It moves in the direction of negligible risks. It clarifies EPA authority in a number of areas like setting expiration dates for tolerances, demanding the development of practical monitoring techniques, establishing fees to support some of the related activities. All of these are very useful and helpful to the Agency.

On the other hand, as we look at the specifics of the bill, we have a number of concerns, and I would try very, very quickly to touch on them. Essentially, our concern is that, as drafted, it is too proscriptive and rigid, and we will work with the committee in suggesting some ways that these sharp corners, if you will, could be made more workable.

As it relates to the constant standard for tolerances, the bill as drafted is responsive to the National Academy of Sciences report, "The Delaney Paradox." Again, we commend that, and we think that a move toward a negligible risks standard and away from a zero risk standard is a much needed step in coming into compliance with where the science presently is.

However, as we look at the specifics again, we get into problems, and, again, I go back to this fundamental issue on where benefits should fit in the process as it relates to pesticide registrations. I would cite at least two examples that I think may be worth some thought as we try to clarify those.

One of them deals with our desire to have the legal authority to register a pesticide which would replace a riskier pesticide, even if the pesticide that was coming on line constituted some risk in the real world as we project those risks with these models and probabilistic statistics.

Second, I would like to see the Agency have the authority to deal with situations in which you are looking at a kind of health-health or risk-risk tradeoff. An example of that would be something like ethylene oxide, a fumigant used on spices basically to prevent pathogenic organisms from growing on these materials. And there is a true benefit in terms of public health, and we need some capacity to look at those factors as we look to the future.

In terms of the negligible risk standard, the specific language in this proposal, again, is just too proscriptive. A margin of safety of a hundred as required in the act is the general way we do business and in keeping with the mainstream thinking in the scientific community. However, under a number of circumstances, we use margins of safety of 10 as part of the generally accepted principles of toxicology at this point where the data is better and we have human data. These are important flexibilities that a strict enactment as drafted might limit our ability to use the best science in the future.

Similarly, the negligible risk for a carcinogen as stated at one in a million is also subject to a qualification that reads something like, "And it is not likely to cause or contribute to any additional adverse human health effects." In staff discussions, we have been led to think that that may mean that the intent was that we would not allow a single additional cancer in the way we project risks. If that were to be the case and if we were to look at a food residue for which, say, a hundred million people might be covered, the practical consequences of that would say negligible risk was not one in a million, it was really one in a hundred million, which is an incredibly tiny risk. Again, before we move into that, I think we need some discussion to ensure that we fully understand the consequences of such action.

In the area of exposure, you ratify the Agency's present policy of using the best available data on the actual exposure levels people would consume on the basis of looking at health risks and doing risk assessments. But the bill goes on to propose that that level then would become the basis of setting the tolerance. Since, as a practical matter, the levels of residues on food for the most part dissipate with storage as it moves through the food chain, we could end up with a tolerance that either would have to be enforced at the supermarket, which is the wrong place—if you are looking for it in the supermarket, the food is gone before you are going to get the test results back—or we have to back up the food chain with levels that would end up probably having some food considered adulterated, even though by the time it got to the consumer, it would not exceed these negligible risk levels. Again, it is just too tightly defined to be implemented very effectively.

The language as it relates to population subgroups, again, we think this is a step in the right direction. It is consistent with our recently improving analytical ability to look at subgroups of the population, like infants and children. Very important.

On the other hand, as drafted it is kind of vague as to what it really means. If it were to mean that we should set standards to protect vegetarians, for example, who have a different consumption pattern than most of the people in the United States, or that we were to try to identify the most sensitive individual, the impacts of such changes could be very, very severe in terms of the way we normally do business. Again, clarification and some linking of the proposal to its probably impacts in implementation we think would be helpful.

As it turns on inerts, we share the view that inerts are potentially a problem, and we, in fact, are implementing a strategy to sort out the worst of them to and to get them out of the products as registered. But, again, if enacted as drafted, which would require us to say that any inert that did not receive a GRAS designation—generally accepted as safe—would require a tolerance, we are overwhelmed by the numbers.

Briefly, let me run you through that. There are about 1,200 inerts. About half of those are used on food. Of the 600 that are used on food, our estimate is about a hundred would meet the way generally accepted as safe is defined in the current regulatory parlance. That would mean that we would have perhaps as many as 500 active ingredients for which we would have to set tolerances for each and every crop that they are used on or could be used on. That gets to be a workload of some 5,000 tolerances. Our best guess is that the workload that would be required in terms of FTE's—the way we count work years in the Government—would more than double our current work force, and is clearly beyond our capability to manage. And it would come at the same time that we are actively pursuing the implementation of the 1988 amendments, which are focusing our attention on what we think is a much more important public health issue—that is, the reassessment of the pesticides that were registered in the past before the contemporary standards were available to us.

What we are doing with inerts is we have sorted out the universe of 1,200 into several categories.

The most risky, which we called of toxicological concern, we, in fact, have used the data call-in process to go back to the registrants and say you have three choices. You may either reformulate the product in order to get rid of the offending inert; or relabel it so that people understand exactly what they are being exposed to; or begin to develop the data which would be necessary to develop a numerical tolerance for that material. Faced with those choices, virtually all of the first generation of products are reformulating. So we are getting the most worrisome of these inerts out of the formulation process with a manageable workload.

For the second tier—that is, those which we viewed of concern—we are using the authorities under the Toxic Substances Act to collect additional toxicological data which may not have been published so we can better assess the potential risks associated with those chemicals. In this fashion, we intend to work our way through the full list, and that is our current plan. Again, we think that in view of the overall problems facing the Agency that this is an effective strategy and consistent with our perception that, generally speaking, the inerts do not constitute significant risks.

To conclude, then, we commend the introduction of the bill and the public dialogue around it because these are important issues that really need to be addressed. After the public reaction to the perception of risks associated with the use of ALAR in apples, we all clearly understand that the American public is looking for a much higher level of protection in terms of pesticide residues of food, and we need to get on with that. Again, though, to the specifics of the bill, our concern is principally with the rigidity, the absence of operating flexibility for us, and we look forward to working with the committee staff to see if we can improve these elements of the bill.

Thank you.

[The prepared statement of Mr. Kimm follows:]

PREPARED STATEMENT OF VICTOR J. KIMM

Good morning, Mr. Chairman and Members of the Committee. I am pleased to be here to discuss S. 722, the proposed Food Safety Amendments of 1989. This bill would substantially rewrite the provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA) that concern pesticides. The introduction of this bill, and these hearings on it, will focus the much-needed debate on how the government should regulate pesticide residues in food. The bill has both strong points and weaknesses.

Before discussing the specifics of S. 722, I want to describe two paramount concerns that, in my view, must be satisfactorily addressed in any new food safety legislation. First, there must be consistency and compatibility between the two statutes under which EPA regulates pesticides -- the FFDCA and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Under FIFRA, EPA regulates the sale and use of pesticides through a program that requires the pre-market approval of a license (registration) for the pesticide. Sale of the registered product is allowed only if the product has the approved composition, packaging and labeling. Moreover, under FIFRA, it is illegal to use a pesticide in a manner other than authorized by the product's labeling. Basically, registration is allowed only if the product's use does not cause "unreasonable adverse effects on the environment." FIFRA directs EPA to weigh the risks against the benefits derived from use of a pesticide in applying this standard.

EPA is responsible under the FFDCA for setting tolerances (maximum permissible residue levels) for pesticides in or on food and feed commodities. EPA establishes a tolerance for residues of a pesticide in or on a particular food commodity only if toxicological data, considered together with available data on the levels of residues on food and food consumption patterns, indicate that the residues expected under the tolerance will not pose an unacceptable risk to consumers. Tolerances established by EPA are enforced by the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), which conduct surveillance monitoring for the purpose of tolerance enforcement.

EPA simply cannot perform its duty effectively and responsibly if the statutes it must apply are incompatible or inconsistent. It is essential, therefore, that FFDCA and FIFRA both work together so that EPA can run an effective and efficient regulatory program.

Second, it is vital that a regulatory agency must be provided a degree of flexibility to carry out the broad mandates of the statutes it implements, particularly when regulation is based on scientific areas in which knowledge is constantly expanding and old truisms are frequently challenged. A lack of flexibility could make it difficult, if not impossible in some instances, for EPA to comply with the law's demands or to reach sensible regulatory results.

As I will make clear in the rest of my testimony, I think that S. 722 falls short of the mark in both of these areas. There must be better coordination between the requirements of FIFRA and the FFDCA than S. 722 would achieve. Moreover, EPA must have greater operating flexibility than S. 722 would allow.

S. 722 attempts to address several of the problem areas in the pesticide provisions of the current FFDCA.

1. First, it brings all regulation of pesticide residues in food under one set of provisions of the FFDCA.
2. It advances the concept of negligible risk as the appropriate standard for establishing legal residue levels in food.
3. The bill recognizes the need to clarify the Agency's regulatory authority in several areas and to provide a more efficient administrative process for tolerance-setting. For example, the bill provides clear authority for EPA to set expiration dates for tolerances; to require data; to reevaluate existing tolerances and exemptions; to demand practical methods of residue analysis; to collect fees for the maintenance of tolerances; and to allow food which contains residues from legal use of pesticides to clear the food supply

channels of trade after a tolerance has been reduced or revoked.

4. The bill directs EPA to look at inert ingredients and establish tolerances for the residues of inert ingredients in food.

I would like to expand on the general points I've just mentioned by illustrating some of the positive aspects of the bill and some of the areas where it appears too restrictive.

1. **The Consistent Standard**

This clearly is a major step in the right direction. As the National Academy of Sciences made clear in its 1987 report, Regulating Pesticides in Food: The Delaney Paradox, there is no scientific justification for a system that has one risk standard for pesticide residues in raw foods and a different standard for the same residues in foods that happen to have been frozen, dried, or cooked. As the Academy pointed out, the current law's different standards have required decisions that just do not make sense.

Likewise, it is important to apply the same standard to old and new pesticides. Obviously, from a scientific standpoint, a pesticide isn't riskier because it is new; in fact, pesticide manufacturers strive to develop new pesticides that are less risky. However, the current system sets rigid criteria for establishing new clearances for pesticides -- criteria which are sometimes impossible to meet. S. 722 reflects an intent to apply the same standards to reviews of existing and proposed tolerances. For the most part, I believe the legislation achieves this goal but, in some cases, the legislation could exclude new chemicals from the marketplace, or delay their entry, even though they are safer than current pesticides.

Unfortunately, the standard proposed in the bill is not compatible with FIFRA. Thus, the issue of inconsistent statutory standards previously encountered with the Delaney Clause is not fully resolved and is, in fact, intensified. Unlike last year's bill which had some provision for the consideration of benefits, under the current bill, the standard applied for establishing or maintaining a tolerance is "negligible risk," and no consideration of benefits is allowed. Since FIFRA requires the weighing of risks and benefits, the long-standing contradiction between FIFRA and FFDCA would be continued. As stated previously, we believe the FIFRA risk-benefit standard is the appropriate standard for making regulatory decisions on pesticides.

The practical effect of conflicting statutory standards would be that, in some cases, EPA could be required to revoke or substantially lower a tolerance, because the risk is greater than negligible, even though EPA might judge the risk to be outweighed by the benefits of that pesticide to society. For example, ethylene oxide is a known carcinogen. It is used to fumigate spices to destroy microbial infestations that cause human illness.

Shouldn't these benefits be taken into account in making decisions about the tolerance for ethylene oxide on spices?

In the broader sense, should we ignore the consequences of changing the availability or price of produce, either seasonally or more generally, due to reduced pesticide availability? These changes could have an impact on the diet of the nation, or of various sub-groups within the nation, including low income groups for whom food costs are a larger percentage of their expenditures. Recently, the National Research Council concluded that consumption of fresh fruits and vegetables is important in the prevention of chronic disease based on human epidemiological data. Shouldn't benefits such as these be part of the decision-making process?

2. The Negligible Risk Standard

I note the adoption of a negligible risk standard -- it is clearly more reasonable than a zero-risk approach. However, the bill is overly restrictive, both in setting criteria for determining whether a particular risk is negligible and in attempting to set forth just how EPA should calculate risk levels. For example, the bill defines an ample margin of safety as 100. Although 100 is the margin of safety which the Agency typically has selected for pesticides with adequate data bases, there are instances in which a smaller margin of safety such as 10 may be appropriate. This is the case for certain organophosphate compounds where the effect of concern is cholinesterase inhibition and the data base is sound, including some human data.

Knowledge is advancing rapidly in several scientific areas that bear upon risk assessment, and the bill should give EPA discretion to adopt new scientific methods as appropriate, rather than attempting to specify precisely what methods should be used to carry out the various steps in a risk assessment such as converting animal diet dose levels to human dietary equivalents. To lock the risk assessment process into place by statute will make it impossible for risk assessments in the future to take advantage of developments in our knowledge of carcinogenesis and other biological effects.

I am also very concerned that the negligible risk standard is unnecessarily stringent. As you know, EPA and other federal agencies have stated that chemicals which are potential human carcinogens pose a "negligible risk" if the increased risk from lifetime of exposure is on the order of one in a million or less. S. 722 codifies this standard and then adds a second criterion: the lifetime dietary exposure "is not likely to cause or contribute to any additional adverse human health effects." I understand that this language means that it is not likely there will be an additional cancer case in the entire U. S. population from the residues of a pesticide in food. This interpretation of the negligible risk standard goes far beyond EPA's current policy and, if enacted, would have a dramatic impact on the availability of pesticides to the agricultural community.

Finally, I wish to note that six years after enactment, S. 722 would establish a new and apparently more stringent negligible risk standard. While the Agency finds the meaning of the new standard unclear and thinks it should be clarified, we think that the new standard could further limit the availability of important agricultural pesticides. We are still studying the impacts of the "negligible risk" standard contained in the bill and cannot speculate on the precise nature or extent of these impacts.

With regard to the exposure side of the risk assessment, the bill correctly identifies key issues but again treats them in ways which are problematic.

Actual residues. For example, the bill acknowledges that if reliable data are available on actual residues in food at various stages of production and distribution from farm gate to the consumer's table, these data may be used to calculate dietary exposure. This tracks the Agency's current practice. We have reliable data on a number of pesticides, and they usually indicate that the actual exposure levels are much lower than would be calculated by assuming residues to be at tolerance level. When they are available, we use such data in calculating risk. However, S. 722 would require the Agency, if it uses such data, to set the tolerance for a commodity at the level used in the risk assessment, rather than at the levels found on the commodity when it first enters commerce (at the "farm gate"), as is done currently.

While it is important to assure that levels at the point of consumption do not exceed the levels used in the risk assessment process, setting a tolerance at this level can cause significant problems. If the Agency were to set the tolerance at the level expected at the point of consumption and used in the dietary risk assessment, a large proportion of the treated crop will potentially have residues above the tolerance, and the crop could be subject to seizure at the farm gate even though use of the pesticide was legal. Alternatively, if a farmer must meet the lower tolerance at the farm gate, the farmer would likely need to alter the use pattern of the pesticide, for example by lowering the application rate, in ways that may significantly reduce the efficacy of the pesticide.

I also do not believe the solution to this problem is to enforce the "actual residue" tolerance only through grocery store monitoring. First, if a violative residue is found in a food sample taken from a supermarket, FDA would almost never be able to stop the other food in the sampled lot from reaching a consumer because the food would likely have been sold before the analysis was complete. Thus, such an enforcement scheme would give virtually no protection to the consumer. Second, it is very difficult, if not impossible, to trace violative residues from a grocery store back to the source; it is much easier to discover the source of an illegal residue if the sample was collected and analyzed shortly after a commodity left the farm gate. Finally, in some cases actual residues eaten by consumers will be lower than residues found at the point of sale because consumer handling of the commodity -- cooking a potato, for example -- would further reduce the residues.

In sum, we think the Agency's current approach, distinguishing between the tolerance level and the levels of actual residues used in risk assessment, is sound and should be continued. We agree that it is important to assure that the levels found in food when consumed do not exceed the levels used in the risk assessment process. There are a number of ways this assurance can be provided short of the approach contained in S. 722.

Population subgroups. The bill also requires the Agency to estimate risk to "identifiable" subgroups of the general population. Tolerances could be established only if the risk to each such group was negligible.

Again, the general idea in the legislation is consistent with EPA's current policies and practices. In setting new tolerances and reviewing existing tolerances, EPA is concerned about protecting sensitive subpopulations. EPA understands that some subpopulations -- especially infants and children -- receive higher than average exposure from certain foods. To guard against possible problems from such higher exposures, EPA now routinely calculates and considers both a composite lifetime exposure for an average individual, as well as exposure values for over 20 subpopulations with potentially higher exposures -- including infants and children. Thus, EPA's analysis of pesticides in the diet takes into account that children and infants typically eat more food in relation to their body weight, and more of certain types of food, than the average adult. Using these exposure estimates, EPA evaluates average lifetime risk, as well as the risk for subpopulations with higher exposures. Generally, EPA bases its tolerance decisions on the composite average lifetime risk which includes the proportionately greater exposure that may occur in childhood. The calculations for other subpopulations allow us to ensure that no particular group receives exposure which is likely to cause unreasonable risks. This sophisticated approach, which allows us to account for subpopulations, is the result of improvements in the process which have been implemented over the past several years. We will continue to apply this approach systematically to the reevaluation of old chemicals during the implementation of FIFRA 88 amendments.

S. 722 clearly allows EPA to continue its current policies and practices, but it is unclear whether the legislation would require EPA to consider additional groups. For example, would the requirement to consider "identifiable" subgroups force EPA to calculate separate exposure estimates for vegetarians or people with other special diets? We believe it is important to preserve in the legislation EPA's authority to determine which populations should be considered. The bill should also give EPA flexibility in deciding which subpopulations to consider in determining if a pesticide meets the "negligible risk" standard. For example, if a pesticide may cause birth defects, the population potentially at risk is women of childbearing age; it is not appropriate to consider subgroups of infants and children.

3. Clear Authority And Administratively Efficient Process

Deadlines. The Agency's authorities and duties are clearly set forth in a number of sections of S. 722, but unfortunately, the legislation would have major adverse impacts on the Agency's current resources. Many of the deadlines in S. 722 are impractical and, in some cases, may be impossible to adhere to. For example, it is totally impossible to meet the deadline for reassessment of tolerances within 90 days to determine whether available data are sufficient to conclude that "there is reason to believe" that a pesticide residue may pose a greater than negligible risk. There are thousands of tolerances for over 300 different active ingredients which would have to be examined against the new standards using the new assessment methodologies.

EPA is currently in the midst of a comprehensive reassessment of tolerances as part of the reregistration program under FIFRA. This program involves the reevaluation of all pesticides registered before October 1984 against current scientific standards. Under FIFRA, EPA must complete this task in approximately 9 years. We know from experience that we simply cannot meet the deadlines that S. 722 would impose.

As with the statutory standards and procedures, it is important that the deadlines under FIFRA and FFDCA be compatible. We are still analyzing the workload implications for EPA from S. 722. But our preliminary impression is that the schedules and deadlines of S. 722 do not mesh well with the schedules imposed on the Agency to reregister pesticides under FIFRA. In sum, while attempting to provide EPA with new and clearer authority, the unrealistic deadlines amount to a blueprint for failure.

Fees. The revised section 408 directs the Administrator to establish fees to cover the cost of establishing and maintaining tolerances required under the section. EPA should be able to charge user fees to recover all costs of activities required by other sections of S. 722, which would not be codified in section 408.

New tolerances for cancelled/suspended pesticides. We believe the current statute already allows EPA to set new tolerances or action levels after cancellation or suspension of a persistent pesticide. In some cases, residues of such pesticides may be unavoidable in commodities other than those for which tolerances existed. Such residues should also be provided for. For example, persistent pesticides sometimes remain in surface waters and sediment as a result of past legal use, and these residues in turn end up in fish. They may also occur in crops planted in land used previously to produce other crops that were treated with the pesticide.

In addition, the requirement to modify such tolerances at least once a year will result in much work for the Agency with little practical effect for such persistent pesticides as the chlorinated hydrocarbons. Typically, residues for such pesticides do not decline fast enough to warrant annual readjustments.

Expiration dates. Explicit authority for establishing expiration dates for tolerances is needed. Although the Agency has established tolerances with expiration dates, registrants have questioned our authority to do so, and this provision would make the authority clear.

Usable methods of analysis. The Agency agrees that it is essential for the enforcement agency (FDA or USDA) to have practical methods of analysis. We support the increased development of multi-residue methods. We also welcome the FDA's pre-approval review of methodology proposed by the pesticide registrant for tolerance enforcement. We think it is important to allow the U.S. Department of Agriculture to perform such a review for enforcement methods used for meat, poultry and egg products, which are under its jurisdiction. However, we believe the current statute is adequate to address these issues.

4. Inert Ingredients

Recognizing the need to give attention to inert ingredients of pesticides that may remain as residues on food, S. 722 would establish comprehensive new standards for inerts. We believe, however, that the approach would create more problems than it would solve. Under S. 722, the only inert ingredients that would be allowed for food use are: (1) inerts "generally recognized as safe" (GRAS), (2) inerts that are essential for the working of a particular active, and (3) inerts for which it is scientifically not feasible to replace with GRAS inerts. Inerts meeting the second and third criteria would require tolerances. (Under EPA's current policy, all of these inerts are exempt from the requirements of a tolerance. Such exemptions authorize any amount of the residue to remain in food.)

Unlike the provisions applicable to active ingredients, the sections of the bill covering inerts contains no provision for a transition from current law and policy. Thus, effective on enactment, all residues of inert ingredients on food would be illegal, and the food adulterated, unless the inert were GRAS. As a practical matter, we would not expect FDA or USDA to attempt to enforce such a provision, but considerable confusion and concern would likely exist.

All of the inert ingredients that are currently exempted from the requirement of a tolerance -- these are approximately 600 of the 1200 inert ingredients in pesticide products -- would require tolerances, unless they could be declared GRAS. Since we expect fewer than 100 inerts could be declared GRAS, there could be 500 or more inerts which would require new tolerances. We predict that the requirement of establishing a tolerance for each inert on each food would have tremendously disruptive effects. First, we believe, based on our experience requiring data on inert ingredients, that few food use inerts would be supported by the data necessary to establish tolerances. Thus, we anticipate significant disruption as products are reformulated or abandoned as a result of these inerts provisions.

Second, there will be a significant new burden on the chemical industry to generate additional data. Since an inert ingredient would need a tolerance for each food to which it was applied, companies would need to conduct hundreds of new toxicity studies and thousands of new residue studies to establish necessary tolerances. Finally, EPA would face a deluge of new tolerance petitions, as well as thousands of applications to amend registrations or register new products reflecting the new pesticide formulations registrants would develop, as the number of acceptable food use inerts shrinks. EPA would need a tremendous increase in resources to manage these actions.

In addition to the confusion, disruption, and resource impacts likely to flow from the inerts provisions, another possible consequence is an increase in risk to worker populations and higher residues of the active ingredient in food. By forcing reformulation with a GRAS inert, higher proportions of active ingredient might be required. Such products might still meet the "negligible risk" standard for food, but cause the product to be highly toxic to applicators or result in higher food residues.

These observations simply underscore my initial point -- it is imperative that the provisions of FFDCA and FIFRA be compatible. While I have no objection to adding provisions in the FFDCA which logically address inert ingredients, substantial modifications would be needed to make them workable. In addition, FIFRA may also have to be amended so that the two laws work reasonably together.

Although we are critical of the approach to inerts taken by S. 722, we do not think inerts should be ignored. In fact, the Agency has stated its concern regarding the presence of hazardous inert ingredients in pesticide products in a Federal Register notice published on April 22, 1987. Our strategy for dealing with inert ingredients involves separating the existing inert ingredients into categories based on hazard and focussing first on the most hazardous, the "Inerts of Toxicologic Concern." This category includes all chemicals for which there is some evidence of carcinogenicity or which are known to be developmentally toxic, neurotoxic, or cause some other chronic effect. We have encouraged registrants to eliminate these inerts from their products. If they do not, however, we have also required that they submit data to support the establishment of a tolerance, and we suspend the registration of products containing such inerts if we do not receive the required data. As a result of these actions, we expect relatively few (if any) of these inerts to remain in pesticide products; those that do will comprise a greatly reduced workload for the Agency. The Agency plans to require the data and assess the risks from the rest of the inerts, in order of priority based on hazard. This is a sound approach which is resource efficient and protective of public health, since in our view most inerts are not likely to pose dietary risks.

Thus, we believe that new food safety legislation should recognize the differences between inert and active ingredients in pesticide products and should set appropriate standards and priorities for dealing with each of these. While it is reasonable to require very stringent health standards for pesticide active ingredients which generally are designed to act as poisons to particular pest species, we believe that inerts do not, in general, pose high risks and less stringent standards are appropriate for most inerts.

CONCLUSION

While there are positive features of the bill, we do think that the bill must be significantly revised, especially in the area of operating flexibility, in order to have a regulatory program that is administratively workable. In many respects, I believe that S. 722 represents a step backwards from last year's bill, which itself had significant problems. In fact, I would prefer to operate under the current law -- with all of the difficulties that involves -- than attempt to implement S. 722.

Finally, I wish to note that my comments today do not represent an exhaustive analysis of the bill; I have discussed only the major provisions and policy components. There are many minor points that must be ironed out if we are to have a workable piece of legislation. Cooperation among us all should lead to significant and needed improvements in the FFDCA.

The **Chairman**. Mr. Parnell.

Mr. **Parnell**. Thank you very much, Mr. Chairman and members, for the opportunity to appear before you today to discuss S. 722.

The U.S. Department of Agriculture takes very seriously its obligation to protect the public's interest and the food that it consumes, and we believe that Americans have the right to a safe, wholesome, abundant, and affordable food supply.

While the authority for determining safety of agricultural chemicals rests largely with EPA and with FDA, the U.S. Department of Agriculture certainly has a defined role, a very definite role, and we take that very seriously. We have the responsibility for many aspects of production, marketing, and distribution of food; and, in addition, USDA has the regulatory authority for inspection and inspection responsibility for all meat and all poultry. Much of the effects of the actions that are taken by EPA and FDA, however, manifest at USDA and in the farm community, in the agricultural community.

While USDA accepts the shared responsibility for the safety of our food supply and for the public's confidence in that supply, we believe that the predominance of scientific evidence based on actual residue surveys today suggest that our food supply is absolutely safe. It does not address the issue of the public's confidence in that food supply, but we sincerely believe that all of the scientific evidence available today, based on actual residue, suggests that our food supply is, in fact, safe.

We agree that any pesticide that is scientifically proven to be unsafe, unsound, should not be allowed to be on the market, and if we find those that are on the market that prove to be detrimental, they should be removed. However, the judicious use of chemical tools——

The **Chairman**. If I may interrupt, this is an extraordinary statement to start off with, that pesticides have to be proven to be unsafe. I mean, that is an amazing concept. Is this where we are in terms of pesticides and other food products? That we have to prove that pesticides are unsafe in order to prohibit them from being consumed by the American public is a concept I cannot let just go by without questioning. Others may differ with me on that, and I want you to continue your testimony. But that is something which we certainly have not been willing over a long period of time to accept.

Mr. **Parnell**. Well, I can certainly appreciate your view, Senator, and we can talk about the more. I will be glad to talk, privately or otherwise, on that one issue. But there is a lot of scientific data currently present.

I guess my point here is that we rely on science rather than emotion, if we can, and to try to come to grips with what has gripped our country in terms of a phenomenon that leads them to believe that, in fact, our food supply has a problem.

A point that I hope is not lost in the reaction and the conversation today is one that was well stated when the National Academy of Sciences released its report in 1988 entitled "Diet and Health—Implications for Reducing Chronic Disease." The fact that Americans are living longer "suggests that our society as a whole is not facing a health crisis posed by environmental agents." The National Academy of Sciences committee, in making their recommendation to consume five or more——

The **Chairman**. That is extraordinary. We know that 85 percent of the cancers are caused by environmental factors. We have a long history in the Senate, as chairman of the Senate Committee on Labor and Human Resources, that cancer is basically caused by environmental factors. This has been demonstrated, testified to by the Director of the National Cancer Institute. For you to argue otherwise, unless you are able to back that up with scientific information, runs completely contrary to everything that we have heard from the director of the National Cancer Institute.

Mr. **Parnell**. Senator, I would only submit to you that—and I do not wish to be argumentative, and I appreciate your point of view. I am talking basically about——

The **Chairman**. It is not my point of view. It is the Director of the National Cancer Institute's point of view.

Mr. **Parnell** [continuing]. —fresh fruits and vegetables. We are talking about cancers induced as a result of eating those commodities. I think scientific evidence suggests that it simply is not the case.

The National Academy of Sciences, when they released their report to eat more vegetables and fresh fruits, five or more servings each day, took into consideration the account that the potential exists that they could be consuming more pesticide residues if, in fact, they were on the product in the first place. But the expert body's conclusion was—and I am sure that you are aware—that the benefits from consuming large quantities of fruits and vegetables exceed any potential of any risk that they could calculate.

USDA approves of the elimination of the Delaney clause, or the zero-risk requirement. I think it is common knowledge that this is not a society where zero risk, absolute zero risk, is anything that is available to us. There are risk-risk determinations that have to be made. We believe that negligible risk must be recognized and operationally defined by science, by good science, so that we have manageable regulatory schemes that are workable.

The current method for EPA's determination of risk is generally based on multiple worst-case assumptions, ending up with a truly conservative projection. Current language in S. 722 would make it even more difficult.

Risk assessment is a scientific tool intended to estimate the significance of a potential hazard, but not to definitively indicate real dietary risk or to predict deaths caused from cancer.

We believe that agricultural chemicals do have significant benefits, and we need to discuss those as well. This is another point on which USDA must differ with the pending legislation. Let me explain by use of example. There is a case of many opportunities to use chemicals whose recognized worst-case risk assessment may exceed the one in a million criterion. However, the elimination of the use of the chemical would lead us in a direction of using others that are available and would fit the negligible risk, as it is defined in the bill, but may pose other significant environmental concerns. I think that balance is a point that we want to make definitively if we can.

The reasoned and flexible approach in considering risk/benefit is useful and necessary. Risk/benefit balancing is something that has been excluded from S. 722, and we believe that that should be included so long as it is scientifically based.

Another aspect of the bill as currently written which the Department finds untenable is the requirement of the aggregate negligible risk standard, and EPA can best define their concerns when we deal with aggregate negligible risk. Additionally, the bill would require that dietary exposure to chemicals be calculated based upon the maximum amount of residues that could possibly be expected to occur if people used all pesticides in maximum amounts, according to the label. And I think we have significant evidence that suggest that that does not occur.

We believe that if pesticide use was eliminated or greatly reduced without practical alternatives, production losses would occur, and the cost of agricultural production and marketing could dramatically increase. We think this has a connotation on food prices, certainly could conceivably affect the lower economic status populations because of increased food prices, and the economic well-being of the very individuals that our Government works so hard to support could be in jeopardy.

We thank you for the opportunity to testify, and I would be happy to take questions.

[The prepared statement of Mr. Parnell follows:]

PREPARED STATEMENT OF JACK C. PARNELL

Mr. Chairman, and Members of the Committee, I welcome the opportunity to appear before you today to discuss S. 722 entitled the "Food Safety Amendments of 1989."

The U.S. Department of Agriculture (USDA) takes seriously its obligation to the American people for the safety of foods consumed. We believe that Americans have the right to a safe, wholesome, abundant, and affordable food supply.

As the Department with responsibilities for many aspects of the production, manufacture, marketing, and distribution of food, we have a role to play.

The Environmental Protection Agency (EPA) has the authority for determining the safety of agricultural chemicals and setting tolerances for their use, while the Food and Drug Administration (FDA) monitors residues for all foods with the exception of meat and poultry. The USDA has the regulatory authority for the safety of meat and poultry products. Our charge is to apply and enforce the safe application of pesticides and other chemicals for plants and food-producing animals. We rely on the judgment and scientific assessments of the EPA and the FDA to determine regulatory limits for chemical use in food production and marketing.

The USDA accepts the shared responsibility for the safety of the food supply and for the public's confidence. The predominance of scientific evidence based on actual residue surveys suggest that our food supply is absolutely safe.

We agree that any pesticide that is clearly scientifically-proven unsafe should not be on the market. However, the judicious use of chemical tools is a major contributor to an abundant, affordable, and high quality food supply.

A point that must not be lost in our reaction to the current concerns about agricultural chemicals was well stated in the recently released report of the National Academy of Sciences (NAS) entitled, "Diet and Health -- Implications for Reducing Chronic Disease." The fact that Americans are living longer "suggests that our society as a whole is not facing a health crisis posed by environmental agents." The NAS Committee, in making their recommendation to consume five or more servings of fruits and vegetables each day, took into account the fact that this could potentially increase consumption of certain chemical residues, if present. The expert body's conclusion was that the benefits from consuming large quantities of fruits and vegetables exceed any potential increased risks.

If pesticide use was eliminated or greatly reduced without practical alternatives, production losses would occur and the cost of agricultural production and marketing would dramatically increase. This would translate to decreased food availability and higher prices for consumers. The increased food prices could severely affect lower economic status populations and could repress the economic well being of the very individuals our government works so hard to support.

The USDA approves of the elimination of the Delaney Clause or the "zero risk" requirement. The National Academy of Sciences (NAS) in their 1987 report entitled, "The Delaney Paradox", recognized that zero risk does not exist. Negligible risk must be recognized and operationally defined by good science.

The current method for EPA's determination of risk is generally based on multiple worst case assumptions, ending up with a truly conservative projection. This bill exacerbates this worst case risk assessment.

Risk assessment is a scientific tool intended to estimate the significance of a potential hazard, but not to definitively indicate real dietary risk or to predict deaths caused from cancer. The USDA endorses the proper use of risk assessment as well as the general movement toward reduced and strategic use of agricultural chemicals. This philosophy undergirds the commendable practices of Integrated Pest Management (IPM) and Low Input Sustainable Agriculture (LISA) programs. The USDA supports these concepts, but must emphatically state that we do not include in that support the abandonment of agricultural chemical use. These technologies employ the use of modest but adequate amounts of chemicals in addition to good production management practices. This policy is a sound one for plant and animal production, as well as for the environment.

Inherent in these good management practices is the understanding that agricultural chemicals do have significant benefits. This is another point on which the USDA must differ with the pending legislation. Let me explain by use of example. Consider the case of an agricultural chemical whose recognized worst case risk assessment may exceed the one in one million criterion. However, the elimination of the use of this chemical would permit the exclusive application of products which fit within the requirement for negligible cancer risk, but may pose other increased risks to the environment. For instance, it may be that the example chemical was not toxic to plants, would not accumulate in the soil, and was not harmful to aquatic life. It would be possible that the replacement chemicals could present a greater risk to human health overall, but would be acceptable as defined by this bill as it is currently drafted.

The benefits of agricultural chemical use, in contrast to common perception, do not accrue only to farmers and chemical companies. The benefits accrue to all consumers because well managed chemical use helps to assure an adequate, wholesome, and affordable food supply. The EPA is currently permitted under their regulations to consider the benefits in evaluating chemicals. The elimination of this ability in EPA's determinations of regulatory limits for agricultural chemicals would severely affect the abundance and wholesomeness of the food supply, and would negatively impact all consumers. The reasoned and flexible approach in considering risk/benefit is both useful and necessary. The USDA strongly supports scientific risk/benefit balancing.

Another aspect of the bill as currently written which the Department finds untenable is the requirement of the aggregate negligible risk standard. This concept would be filtered into the determination of a negligible risk level in establishing tolerances to be phased in over a six-year period. By the end of the sixth year, this stringent risk standard would mandate that the combined risk from all pesticides registered and available for use on a particular crop would, in total, be negligible. Additionally, this bill would require that dietary exposure to the chemical be calculated based upon the maximum amount of residue that could be expected to occur if the instructions for use of the pesticide are followed. This would greatly exaggerate real exposures. If for little more reason than their expense, chemicals are used in agricultural production with prudence.

Risk assessments should be based on actual residue data, actual exposure data, and realistic toxicological and metabolic data. We must encourage the responsible use of the scientific information in risk assessment. The appearance of aggregate risk seems to be a practical approach to ensure the public health. However, in practice, aggregate risk assumes the sum total of worst case scenarios, thereby, distorting the risk assessment further from reality; and potentially ignores important research data.

The Department believes that requirements for approval of new agricultural chemicals should not include unrealistic requests for data, unreasonable time tables, or inordinate controls. Such requirements stifle innovations in the development of new agricultural chemicals that could benefit health.

We also see a problem with respect to the proposed amendment for the definition of "pesticide chemical." Under the bill, pesticide chemicals would include those substances used as a pesticide which is or has been used in the production, storage, or transportation of processed foods and the bill removes the use of such pesticides in processed food from the definition of "food additives," which are regulated under Section 409 of the Federal Food Drug and Cosmetic (FFD&C) Act.

Several acts which the USDA administers, namely the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act, contain adulteration provisions which refer directly to the current provisions on pesticide chemicals and food additives in the FFD&C Act. Unless the USDA acts are also amended, only raw agricultural commodities will be deemed adulterated if they contain a pesticide chemical which is unsafe under Section 408 of the FFD&C Act. We suggest that the definition of these different statutes be reconciled.

The proposal to include inert (non-active) ingredients in the tolerance determination, if the inert ingredients were not categorized as "Generally Recognized As Safe" (GRAS), would greatly increase the scope of regulation. Methods for detecting the inert compounds in addition to the active ingredients would have to be developed before this application became practical. Many inert compounds, by their nature, are not amenable to currently available analytical techniques.

Finally, it must be mentioned that the bill refers only to the Administrator of the EPA and to the Secretary of Health and Human Services, suggesting that EPA and FDA are alone responsible for monitoring pesticide residues in the food supply. The Secretary of Agriculture is responsible for the monitoring and surveillance for those pesticide chemicals which may be in meat or poultry products, for which there is an exceptionally active and successful control program.

Despite our concerns, there are some elements of the bill which we can support -- namely, the elimination of the zero risk requirement for processed foods, which is a positive step forward. However, we must oppose the bill as currently drafted due to its potential impacts. The USDA finds the cost, in terms of potential adverse effects on our food supply, of the unreasonable definition and methods for determining negligible risk in this bill unsupportable.

Certainly, if there is sufficient reason to believe that an existing tolerance for an approved chemical should be reevaluated, the Department believes that there should be a mechanism in place for that review to occur in the interest of protecting the public health. However, to make these proposed changes based on the erroneous assumption that regulatory agencies lack the mechanism to suspend the use of select chemicals on an emergency basis is an inappropriate action. The EPA, the FDA, and regulatory agencies under the USDA umbrella certainly have the capability to act swiftly when there is sufficient scientific basis to do so.

Our common goal is to provide a safe, abundant, and affordable food supply for all Americans. But, in order to do so, we must act and react rationally.

The public fear of cancer from consuming the products of American agriculture is an emotional one and has no foundation in fact. We believe that the public is best served by reasoned and timely regulatory action, greater collaboration by responsible agencies, and a greater outreach to better communicate food safety as controlled by good science.

The **Chairman**. Thank you very much. We have a number of colleagues here, so I will ask the staff to watch for the 10-minute rule.

Dr. Young, first of all, it is good to see you here again. You have always been extremely available to all of us on a wide range of different health issues. I appreciate that very much. We agree on many things, differ on some, but we always appreciate both the frankness and candor of your testimony.

Dr. **Young**. Thank you.

The **Chairman**. On the subject of the benefit versus the risk of pesticides, I think it is clear that the greater use of pesticides has an economic benefit to the manufacturers of the chemicals, number one; and we can quantify the benefits to farmers in terms of increased crop yields. But how does the FDA and the EPA, which I understand work closely, how do you value the benefit of the pesticides to the consumers? More importantly, how are the risks of cancer and adverse health effects valued to allow for a comparison of benefits versus risks?

Dr. **Young**. This is a very difficult and extraordinarily important question. I am sure that EPA can add from their perspective.

In FDA's risk assessment for foods, we focus primarily only on the risk. We do this because our public health perspective deals only with the risk associated from food additives, colors and other substances. In relation to medicines, there is where we do a risk/benefit analysis, and EPO (erythropoetin), the biotechnology drug that was just approved, is a good example of that risk/benefit.

In this case, the only health benefit that I can see deals with the concept that is focused on both in the Surgeon General's report and the National Academy of Sciences Report, of eating abundant amounts of fresh fruits and vegetables. Therefore, for those who are underprivileged and are less well-to-do in our society, the supply of a significant amount of these foods at an affordable price is a very important benefit. But, I honestly cannot go and translate this back one to one to an equation. Unfortunately, this is something that we do not do per se in regards to pesticides, and that is under the arena of EPA. In sum, the benefits primarily are economic, with the exception of the healthful benefits of fresh fruits and vegetables.

The **Chairman**. Mr. Kimm, can you tell us how you quantify the benefits to agriculture and then to the chemical companies, versus the risks, health risks to the consumer of pesticides?

Mr. **Kimm**. Let me try, sir. Fundamentally, what we are trying to do is to look at the net societal benefits. That is an economics term. But basically what we try to do, if we are looking at a regulatory action that would say this pesticide would either be available or not be available, is to try to look at what pest it is intended to control, what alternatives to that chemical might be available, and what are the consequences of having or not having those alternatives. In some instances, there may be alternative registered pesticides where the costs would be increased, such as the cost of production that is very likely to be passed through to the consumer in terms of increased costs of the material.

Similarly, in other instances, there may not be substitutes, and the practical consequences may be a loss of production. These are the kinds of factors which the Agency by statute has been required to develop and quantify to the best that we can as we make these registration decisions. Again, that has been a part of the pesticides law since 1948 or thereabouts.

The **Chairman.** Well, do I assume, then, that you do not have a quantitative formula?

Mr. **Kimm.** There is no rubric. That is right. Yes, sir.

The **Chairman.** So it is basically subjective? I mean, you are in one day; Frank Young is in another day. You get changes in terms of the head of the FDA and in terms of the EPA. People want to know what the standard is. What is the criteria? Is it a seat-of-the-pants' judgment about what an individual feels or believes is the amount of risk that children ought to be exposed to, in terms of what the benefit is both in terms of price and in terms of the benefit to the chemical company?

Mr. **Kimm.** Senator, nothing that I have said talks to the benefit to the—you know, the profitability of the chemical company. Rather, the estimate is to try to look at the effect on the food supply, on the society. Now, obviously, the chemical company is a beneficiary of that.

What we are trying to get is some order of magnitude of the economic consequences of whatever regulatory decision we are looking at. That has to be looked at, our best estimate of the potential risk associated with that chemical, and there are some risks associated with virtually all of the chemicals that we look at. If they were not effective as pesticides—to be a pesticide, presumably they are biologically active.

But there is no single rubric, there is no dollars-per-life-saved, or what have you. It is, in fact, a series of value judgments. Perhaps through this legislation, or other means, if this legislation can clarify the parameters that we should consider or give us some better idea of how to make those judgments, that would be helpful to us.

The **Chairman.** The point is that we try quantify risk in this legislation, of one in a million. We recognize what Dr. Young and others have pointed out that science is changing. We are going to make progress in terms of risk assessment and be able to provide additional kinds of protections and safety. That is part of the oversight function of members of the committee. I find it somewhat troublesome to say, well, we should not take one in a million as a criteria, we may have better science in three or five years which can provider a greater degree of safety, so, therefore, do not write that standard in.

I am concerned obviously, and certainly the American people are concerned, that the risk/benefit determination is pretty much seat-of-the-pants. I do not question your faith and knowledge, and your experience and desire to provide that protection, but without a quantitative formula to measure these risks and benefits, there is certainly a very serious concern among the American people.

Dr. **Young.** Mr. Chairman, if I could now comment, I think the very wisdom of the approach that you have taken and Senator Hatch has taken together on this in identifying negligible risk speaks to the heart of your question. The part that I was addressing is that the fundamental analysis is a risk analysis. The benefits may be looked at as additive when it comes to chemicals, but you are fundamentally dealing with a risk analysis.

The details for the scientific risk analysis are quite good, and the state of the art is improving all the time. That is why I focused on the upper-bound risk today of one in a million, as a good upper-bound risk number. The hard part of your question is the amount of benefits. Therefore, by focusing on risks and allowing EPA some degree of flexibility on benefits, you really are driving primarily at a risk analysis. That is what your upper-bound risk is doing, and I think that supports the definition.

There are good assumptions in the data in the Hart report on upper-bound risks in color additives; the report will show you the state of the art on that.

[The report referred to follows:]

Final Report of the Color Additive Scientific Review Panel
September 1985

EXECUTIVE SUMMARY

The Color Additives Scientific Review Panel was directed to determine whether there was information sufficent to perform a carcinogenic risk assessment on the colors D&C Red No. 19 (R-19), D&C Red No. 37 (R-37), D&C Orange No. 17 (O-17), D&C Red No. 9 (R-9), D&C Red No. 8 (R-8) and FD&C Red No. 3 (R-3) and to evaluate the assessments sent to FDA as part of the petitions for use of the colors for drug and external uses by the Cosmetic, Toiletry and Fragrance Association (CTFA). FDA's Center for Food Safety and Applied Nutrition (CFSAN) has raised a number of questions concerning the scientific bases of any such risk assessment.

There is a lack of human data concerning the colors for making a human health assessment. Clinical and epidemiological studies are extremely valuable in estimating risk. However, because of considerations such as confounding factors and long latency times for human carcinogenesis (during which time exposure information is lost), and the desire to regulate hazards in a preventative fashion, it is often necessary to utilize available animal information in order to estimate risk. Risk assessment, in this regard, can be seen as a "best current guess by scientists", using all the information available often requiring extrapolation from animal studies to man. Improvements in our understanding of the mechanisms of carcinogenic action also improve the process of risk assessment as uncertainties, which arise as a consequence of utilizing assumptions to bridge gaps in information, are replaced by definitive human and animal data. In using the process, however, it is important to appreciate the limitations in it and not focus on the numbers that are generated as much as focussing on the evolving picture of our understanding of the interaction of organism and agent.

In this light, the panel has determined that the CTFA risk assessments for R-19, O-17, and R-9 are consistent with present acceptable usages in risk assessment. CFSAN's concerns are important ones, but they can be addressed by making reasonable, practical assumptions about the possible influence that these concerns have in adding to the uncertainty in the overall risk assessment. The risk assessments are determined for exposure to single chemicals. Excluded from consideration are possible effects from exposure to multiple chemicals, such as co-carcinogenesis, promotion, synergism, antagonism, etc.

A number of general assumptions are made in the process of the assessments that are evaluated. In risk characterizaton, the validity of the assumptions, their impact on total uncertainty and the potential options to address the gaps in understanding that necessitate the assumption are given. The Panel also derived revised risk estimates using more "reasonable" assumptions than "worst-case" situations, for 90th percentile and average exposure.

For those assumptions that are easily quantifiable, the Panel's estimates are less than an order of magnitude lower than the CTFA risk estimates, indicating that the underestimates and overestimates of the CTFA risk estimates tend to balance each other out. The impact of most of the assumptions is not quantifiable.

The assessment for R-3 is complicated by the fact that there is no good skin penetrance study for this color. It was assumed that the penetrance is similar to that of another water-soluble xanthene color, R-19. It is expected that the absorption of the color is not likely to exceed that of the smaller molecule, R-19. Therefore, the risk estimates are similar to the CTFA estimates, but with different reasoning.

The estimates for R-8 and R-37 are different than the others in that there is a lack of any exposure or toxicological information on these colors. The toxicological properties were considered to be similar to the chemically related colors R-9 and R-19, respectively. The risk calculated for these dyes is actually a unit risk, i.e., a risk based on particular unit exposure. The unit exposure used is the exposure estimated from the chemically related color, which, from the production values for the dyes, is likely to have much higher usage.

Exposure to all of these colors from external and drug uses is quite low, especially as a result of exposure through skin. Therefore the risk estimates are low. It is cautioned that usage information is based on a recent survey, and changes in usage will alter the risk estimate.

INTRODUCTION

I. PURPOSE

The charge given the Panel was to evaluate the possibility of performing a scientifically valid carcinogenic risk assessment on the color additives D&C Red No. 19 (R-19), D&C Red No. 37 (R-37), D&C Orange No. 17 (O-17), D&C Red No. 9 (R-9), D&C Red No. 8 (R-8), and FD&C Red No. 3 (R-3) for drug and cosmetic uses. Risk assessments for other toxic endpoints were not considered. The Panel did not consider the weight-of-evidence whether the colors were or were not human carcinogens since it understood that it was FDA policy that an agent which is carcinogenic in some experimental paradigm in any species is to be considered a suspect human carcinogen. The Panel also did not consider whether any agent was carcinogenic in a test appropriate to determine safety, since this was understood to be a decision beyond the scope of its charge. In this framework, the Panel accepted that risk assessments can be performed provided that a number of scientific concerns are taken into account by reasonable and practical assumptions about the effect of certain gaps in information. It also elaborated on important scientific bases of the assumptions used in the assessments and the uncertainties associated with them. This was done against the background of the National Academy of Sciences' Report on Risk Assessment (1), the Office of Science and Technology Policy's document on chemical carcinogenesis (2) and the Executive Committee, Coordinating Committee on Environmental and Related Program's (CCERP) Report on Risk Assessment (3), efforts which are developing a consensus on risk assessment. Finally, it developed revised risk estimates which may be useful.

Since there are uncertainties about both the broad assumptions used in quantitative risk assessment and the specific assumptions used for each dye, it must be understood that the use of a quantitative risk assessment does not imply certainty about the assumptions and conclusions of the procedure. However quantitative risk assessment is the "best guess" based on the scientific information and understanding presently available. The assumptions used in these analyses are based on reasonable and practical constraints on the effects of unknowns, such as constituents in the dyes, etc. The use of criteria such as reasonableness and practicality in making a "scientific decision" may seem incongruous for those who demand certitude and precision, however one has little choice when faced with the necessity of making a timely determination to assist the formulation of a decision on safety except to use the best current science available. Many public health decisions have been, and are being, made without knowledge of the toxic mechanisms involved and without comprehensive databases. In recognition of this, the statutes which discuss public health matters almost always address the question of safety or harm; which are complex health judgments based on knowledge, experience, appropriateness, etc., rather than make specific statements about toxic effects. Finally, it should also be appreciated, however, that there are significant differences of opinion in the scientific community about the magnitude of the uncertainty in quantitative risk assessment (e.g., see 4). Estimates of this uncertainty can vary from fairly small to orders of magnitude. A quantitative risk assessment is not only a number. It is an evaluation of the information about a compound and its toxic effects, frequently in the absence of human data and an evaluation of the uncertainty associated with the estimate or risk that is derived.

In sum, the analyses below are to be approached in the light of using what appear to be the most reasonable and practical assumptions consistent with currently available information and understanding, in conformance with the principles of the developing science of risk assessment, to aid the risk manager in making the decision on safety.

II. STRUCTURE

The report contains a scientific introduction section for major topics being discussed. It then contains a section on the general assumptions used in the risk assessments of the colors. It then proceeds to discuss the risk assessments for each of the dyes involved by discussing major topics for each dye and the color-specific assumptions used with focus on the risk under practical conditions of use and exposure. Each chapter also contains a risk characterization section which discusses the risk assessment of the dye. The final chapter is a summation of the different risk characterizations of the various dyes.

III. CONTEXT

The 1960 Color Additive Amendments of the Food Drug and Cosmetic Act allowed for provisional listing of color additives pending completion of studies to determine whether they were safe for their intended use (5). If safe, they were to be permanently listed for use. The provisional list originally contained approximately 200 color additives. Since 1960, 126 have been permanently listed and 63 removed from the market. There are ten additives left on the provisional list, six of which are under consideration here.

The Center for Food Safety and Applied Nutrition (CFSAN) has been involved in the evaluation of these dyes for some time, and has come to the conclusion that no quantitative risk assessment of these colors can be made (6) for a variety of reasons. On the other hand, the Cosmetic, Toiletry and Fragrance Association (CTFA) has performed risk assessments on the colors and submitted the assessments to the FDA (7-10), complemented by an extensive discussion (commissioned by CTFA (11)) of the merits of the different positions. This panel agrees with CFSAN that there are a number of important scientific uncertainties that must be considered. However, these concerns can be addressed by reasonable and practical assumptions as to their effect on risk.

CHAPTER 1 - GENERAL SCIENTIFIC CONSIDERATIONS

I. CHEMISTRY

This section will discuss some of the general aspects of the chemistry of the color additives. Most of the issues are specific to each color additive, and a discussion of the basic chemistry and synthesis of each of the color additives (R-19, R-37, O-17, R-9, R-8, R-3) is contained in the first part of the chapter on that dye. There is also a discussion which addresses critical issues such as the levels and types of impurities that may be present in the dosing solutions used in the bioassays, the purity of the dosing solutions as percent "pure color" additive, and the chemical and radiochemical purity of the radioactive dosing solutions used in *in vitro* skin penetration studies in the section which discusses these assays. In addition, the quality assurance data regarding the verification of dietary doses used in the bioassays are reviewed, along with data on stability of the colors in feed, and the homogeneity of the diet formulations.

The color additives are members of different chemical classes, with three (R-19, R-37 and R-3) considered xanthene dyes, and three (R-8, R-9 and O-17) considered mono-azo dyes. R-37 is the stearate of R-19, while R-8 is the sodium salt, and R-9 the barium salt, of the same anion.

The colors are not single chemical entities despite their categorization with simple chemical names (*e.g.*, R-19 is frequently termed Rhodamine B), which complicates the interpretation of toxicological information on the dyes. All batches of these colors are certified by FDA before they can be used in commerce. The certification requirements are generally not rigorous. They do not fully characterize the purity of the color (as percent of color additive) or the amounts and variety of impurities that may be present. These impurities could include subsidiary colors (colored analogs which are closely related chemically), side reaction products produced during synthesis, residual starting materials, and possible degradation products (12,13). For example, methods to determine "% color", often confused with "% purity", are based on the reduction of the dye with titanium trichloride or the determination of total color, by weight, using spectrophotometry. Subsidiary colors, thus, would usually be included with the "pure color" as "% color" by these non-specific methods. The certification requirements also specify the levels of some starting materials, volatiles, organic solvent-extractable compounds, subsidiary colors, salts and inorganic contaminants. The methods listed to perform these certification assays are often not state-of-the-art, chemically definitive methods. The specifications are listed in each color chapter, along with a discussion of impurities found in certified lots.

Concerns about impurities in these color additives are real ones, especially when risk assessments are performed on these mixtures termed "certified color additives". As discussed above, the specifications permit certain levels of impurities (13). In addition to these stated impurities FDA (12, 14-19), the report prepared by the Environ Corporation (11), and others (20-25) have speculated on the large variety of possible impurities that may be present as a result of side reactions during synthesis, products from impure starting materials, and, in some cases, degradation products.

The major issue concerning impurities is not what impurities are possible, but what has actually been quantitated in FDA certified lots, particularly those lots used in the bioassays for the carcinogenic effects of the material. Reasonable definitive analyses have been reported for these certified lots by more rigorous methodology than that required by the certification requirements and, in all cases, levels of the starting materials have not exceeded 1% of the color additive (on a weight basis), with the levels of subsidiary colors reported to have been as high as 5%. These two types of contaminants are the foci of concern. Obviously, the impact of these impurities on the risk assessments depends not only on the concentrations of the impurities but also on the carcinogenic "potency" of the materials and, for external uses, skin penetrance relative to the major color additive.

In the case of the starting material impurities, as noted above, the highest concentrations found have not exceeded 1%. For chemicals related to known mutagens or carcinogens (such as the aromatic amines) levels have not exceeded 0.5%. If the starting material impurities were responsible for the carcinogenic effects of the colors they would have to be: 1) highly potent carcinogens; and 2) highly absorbed through the skin. The Environ

Report (11), and the other available data indicate that it is highly unlikely that these impurities could be responsible for the reported carcinogenic effect. In the special case where the color additive may be metabolized to a split product, such as an aromatic amine, and this material is present as a starting material impurity, the bioavailable aromatic amine in humans would be the sum of the dermally absorbed impurity and the metabolic product of the dermally absorbed color additive. Environ (11) and others conclude that it would be unlikely that the contribution from the starting material would be significant compared to that available from the metabolism of the intact color additive. The following section of this report, as well as the chapters on the individual colors discuss what is known about the metabolism of these color additives.

In the case of the subsidiary color impurities, even if the subsidiary color was carcinogenic and present at 5%, its close similarity in chemical structure to the main color would probably preclude large differences in skin penetration rates.

Thus, although impurities cannot be ruled out as contributors to the carcinogenic response of these color additives, it is highly unlikely that they would influence the final risk assessment in any great degree. The issues of impurities are also addressed in the next chapter and in the chapters concerning the individual colors.

Another complication for interpreting the toxicology data is that the colors are frequently used for external cosmetics in a "lake" form, i.e., by extending the dye in a salt form on a substratum of alumina, clay, titanium dioxide, etc. This process presumably makes the dye more insoluble and prevents color leaching, useful in cosmetic applications.

As noted above, specific considerations about the chemistry of the colors, the impurities present, the form of usage, and reasonable scientific assumptions used to address the potential hazards of these dyes are addressed in the specific color chapters.

II. DISPOSITION AND METABOLISM

Studies on the distribution and metabolism of the principal components of the colors have been performed only for R-3 and R-9. Even these studies are not sufficently extensive to decrease markedly the uncertainties in making the risk assessment. The following is a discussion of the basic concepts that should be considered in estimating the uncertainties inherent in risk assessments of carcinogens.

A. Basic Pharmacokinetic Principles: Bioavailability

Most of the mechanisms by which carcinogens are thought to exert their actions may be expressed by a mathematical function that includes the area under the curve of the concentrations of the biologically active substances (AUC) at action sites within target cells and a term that relates the AUC to the response. For example, the number of adducts formed from a dose of parent compound may be expressed by the AUC of a chemically reactive metabolite times an effective clearance term (CL_{ad}) which may or may not vary with the value of AUC (if the term doesn't vary, the number of adducts then equals AUC X CL_{ad}). Thus, the relevant pharmacokinetic factors may be largely understood in terms of how they will affect the AUC of the ultimate carcinogens within the given target cells.

Many factors may govern the AUC of ultimate carcinogens, including the solubility, route of administration and dose of the parent compound. The administration of inducers or inhibitors of enzymes that either metabolize the precursors of the ultimate carcinogens or inactivate the ultimate carcinogen, may also cause major changes in the AUC values. Such analyses require knowledge of the ultimate carcinogens and the pathways by which they are formed as well as the location of the target cells. Indeed, without such knowledge, the proper interpretation of pharmacokinetic studies is difficult, if not impossible.

One of the important factors that may affect the AUC of an ultimate carcinogen is the bioavailability of the parent compound. Several approaches have been used to estimate bioavailability (26), but each has its limitations. Three approaches used commonly are discussed below.

In the first approach, the bioavailability after oral administration of radiolabelled parent compound is estimated by measuring the amount of radiolabel which is excreted into the urine. Any metabolite formed by the intestinal flora that is subsequently absorbed would be considered bioavailable, but the amounts of parent compound and its metabolites in the body that are subsequently excreted into the bile and eliminated in the feces would not be considered bioavailable.

In the second approach, the amount of unchanged parent compound that is eliminated unchanged with the feces is considered to be unabsorbed. This does not preclude the possibility that some of the parent compound is absorbed into the body and, subsequently, excreted into the bile.

In the third, most detailed, approach, the AUC/dose of the parent compound in systemic venous blood after oral administration is divided by the AUC/dose of the parent compound after intravenous (or any other kind of parental) administration. Bioavailability estimated in this fashion, however, reflects not only the amount of the parent compound that is eliminated in the feces without being absorbed, but also the amount of the parent compound that is metabolized by intestinal mucosa and microflora. The estimate also reflects "first-pass effects" in the liver.

"First-pass effects" are related to the average ratio of the rates at which the parent compound leaves and enters an organ during the time of absorption. "First-pass" elimination of the parent compound in the liver reflects the amount of parent compound that is metabolized in the liver as well as the amount of parent compound that is eliminated by the bile but is not reabsorbed.

The primary usefulness of the third approach is to estimate the AUCs of the parent compound in "non-first-pass" organs (i.e., organs that are not served by blood passing from the site of administration to the arterial circulation). Its usefulness is limited when the target cells are in a "first-pass-organ" since, after oral administration of the parent compound, the AUC of the parent compound in the blood through a "first-pass-organ" is usually larger than the AUC in the systemic blood. Usefulness is also limited when the ultimate carcinogen is a metabolite.

Concepts such as "first-pass effects" are also applicable when estimating bioavailability by routes of administration other than oral, such as dermal. After coating a small area of the skin with the parent compound, the AUC of the parent compound in the blood perfusing that area of skin will almost invariably be larger than the AUC of the parent compound in the systemic venous blood. Because the skin contains enzymes that activate some compounds to ultimate carcinogens (27), carcinogenic compounds in cosmetics may occasionally manifest their effects mainly in skin.

B. Effects of Different Doses

The effects of increasing the dose of a parent compound on its AUC will usually be unpredictable. If increasing the dose resulted in a decrease in the fraction of the dose that is absorbed, the AUC/dose values for the parent compound and all of the metabolites formed from the absorbed compound obviously would be decreased. However, if the parent compound underwent an extensive "first-pass effect" after oral administration, increasing the dose may increase the availability of the parent compound as the concentrations of the parent compound approached and exceeded the Km values (i.e., the concentration of a substrate at which the rate of metabolism by an enzyme or the rate of transport by an active transport system is one-half the maximum rate) of the various enzymes in the intestinal flora, intestinal mucosa, liver, lung and the biliary transport systems in liver during absorption of the parent compound. Alternatively, concentrations of the parent compound in the systemic venous blood may approach saturation of enzymes not only in the "first-pass organs" but also in the other organs of the body that contribute to the elimination of the parent compound.

"Dose-dependent" (as opposed to concentration-dependent) decreases in the total body clearance of the parent compound may result from an increased dose which leads to depletion of the cofactors required by enzymes that metabolize the parent compound. These depletable cofactors include phosphoadenosyl phosphosulfate (PAPS) (28,29), uridine diphosphoglucuronate (UDPGA) (29), and glutathione (30). In addition, some oxidation reactions conceivably may be limited by the concentrations of NADP+ and NAD+ within cells, and reduction reactions conceivably may be limited by the the concentrations of NADPH and NADH.

For the AUC of biologically active metabolites (M_{ba}) in target cells, the effects of increasing the dose of the parent compound are even more unpredictable than for the AUC of the parent compound. The effects will depend on which enzyme has the lowest K_m value or which of the cofactors are most easily depleted. For example, if the enzyme having the lowest K_m value catalyzed the formation of M_{ba}, then increasing the dose of the parent compound would decrease the fraction of the dose that was converted to M_{ba}, e.g., a tenfold increase in the dose would result in less than a tenfold increase in the AUC of M_{ba}. Metabolites, including M_{ba}'s, may be converted into either penultimate carcinogens or inactive metabolites by combining with depletable cofactors such as UDPGA, PAPS and glutathione. Cells may become depleted of the cofactor and the effective clearance by this metabolic pathway may decrease. As a result, "dose-dependent" kinetics may occur at high doses of parent compounds even when the concentration of the metabolite does not exceed the usual Km of the enzyme (usually determined in vitro). Changes such as these need not be reflected by marked changes in the pattern of metabolites eliminated into urine or feces or in the AUC of the parent compound in systemic venous blood, and thus are not always detected by the pharmacokinetic studies usually done even when several different doses of the parent carcinogen are used in the study.

C. Strain and Species Differences

Many carcinogens are activated by a set of enzymes collectively known as cytochrome P-450. Although the strain differences in the primary structure of the various isozymes of cytochrome P-450 may result in insignficant differences in substrate specificity (31), there are significant strain differences in the mechanisms which govern the relative abundance of the isozymes. Indeed, there are even strain differences in the inducibility of the different isozymes by various compounds (32). Thus, in certain strains of rats, some isozymes can be easily induced by low doses of benzo(a)pyrene whereas in other strains a similar extent of induction may not be attained even at very high doses. And, even though an inducer may induce the synthesis of cytochrome P-450 in several animal species, the structure and the substrate specificity of the induced isozymes are not identical, e.g. the differences in the primary structure of the various isozymes of cytochrome P-450 are marked in different animal species (33). Therefore, the effects of induction on the pattern of metabolites of a given substrate may differ markedly with the animal species.

D. Heterogeneity of the Human Population

There are many examples of polymorphisms illustrating the presence of genetic differences in humans in the metabolism of drugs and other foreign compounds (34). In addition, there are numerous examples of environmental differences that influence the metabolism of foreign compounds. Even in studies with a small number of individuals, it is not uncommon to find an order of magnitude difference in the total body clearance of a drug. There are even precedents for differences of two orders of magnitude in the total body clearance of drugs (35). In this context it may be important that the activities of the cytochromes P-450 that metabolize benzo(a)pyrene in human placenta can vary by over 400-fold in different individuals (36). Thus results of an animal study may represent some portion of the human population, but they probably cannot represent the entire human population. Indeed, even a clinical study with a selected few humans is not necessarily applicable to the entire population.

E. Scaling from Animals to "Man"

A long debated controversy in risk assessment centers on whether doses used in risk assessment analysis should be calculated in terms of the metameter of amount per body weight or amount per surface area. Perhaps there is some justification for using the amount per body surface area for compounds that are eliminated from the body predominantly by processes dependent on some physiological function (such as glomerular filtration rate in kidney and flow-limited metabolism in the liver) or by metabolism by "specific enzymes" in which interstrain differences in animals and interindividual differences in the human population are likely to be small. But for compounds in which there are marked interstrain differences in metabolism by nonspecific enzymes in animals and marked interindividual differences in metabolism by such enzymes in the human population in different environments, there seems little justification for choosing between the approaches on mechanistic grounds for a first guess. Validation of either approach would be difficult because results would depend on which strain of animals and which group of humans were selected for comparison. Moreover, a difference of an order of magnitude obtained by the two metameters may be trivial when compared to the large variance that may occur in the metabolism of some foreign compounds in the human population.

F. Summary

To achieve accurate estimates of risk, one requires knowledge of the metabolites and the mechanisms by which a carcinogen causes an increase in malignant tumors. Many interrelated factors will govern the incidence of carcinogenesis in a given study. Among these are species, strain, and individual differences in the relative distribution of enzymes that govern the formation of adducts in different tissues. Dose-dependent kinetics may occur, but the effects at different doses will be unpredictable. Environmental factors will also affect the fraction of the dose of the carcinogen that is converted to relevant metabolites.

Oncology has not progressed to the understanding of all these factors even for the animals used in bioassays (37). Even if these parameters were known for the bioassay, however, the probable influence of different environmental and genetic factors, and the heterogeneity in the distribution of these factors in the human population should be appreciated.

III. SHORT-TERM TESTS

As discussed in detail in the OSTP document on chemical carcinogenesis (38), the role of short-term tests in carcinogenic risk assessment is a developing one. Coming out of the general approacn of developing in vitro analyses and rapid tests with definable endpoints, a number of these assays were designed to predict the results of a carcinogenicity bioassay, which, it was believed, was the best predictor of human carcinogenic response. This search has lead to a variety of assay systems with a diversity of endpoints. The existence of so many assay systems (over 100 have been described) reflects both limitations and differences between the assays as well as uncertainty about the mechanisms of induction and progression of carcinogenesis.

There have been some attempts to evaluate short-term test performance. One, the Gene-Tox Program, initially reviewed the literature from 1969-1979 to assess the test systems, and is presently analyzing the database to determine which test, or combination of tests, can be used for screening or need further development (38). The International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC) evaluated the ability of short-term tests to evaluate pesticides (39).

The best study to date, The International Collaborative Program for the Evaluation of Short-Term Tests for Carcinogenicity, used 42 chemicals, supplied as coded samples, and tests in sixty different laboratories, some of which performed the same tests (40). A number of conclusions can be derived from this information:

1) The majority of assays gave a positive result for a majority of carcinogens tested;
2) The hypothesis that a positive response of a carcinogen was evidence of a mechanistic correlation of the test was brought into question;
3) If a non-DNA reactive, noncarcinogenic chemical is submitted to a range of in vitro assays, then a significant proportion of the responses observed will be positive, but meaningless to animals;
4) The correlations between magnitude of in vitro test response and carcinogenic potency are tenuous and apparently of little value;.
5) There was often wide interlaboratory variability for the same test.

Different assays had different sensitivity (ability to detect a carcinogen), specificity (ability to detect a non-carcinogen) and accuracy (both). For instance, reversion in a yeast, Saccharomyces cerevisiae strain XV185-14C (a haploid strain), had a sensitivity of 0.64, a specificity of 0.59, and an accuracy of 0.62, while mitotic recombination in strain D4 had a sensitivity of 0.08, a specificity of 0.77 and an accuracy of 0.36. To put these numbers in perspective, the probability associated with assigning carcinogenicity accurately by flipping a coin is 0.5.

Attempts to place short-term assays in a comprehensive framework have met with varying success. One of the most interesting is a recent attempt based on a Bayesian decision paradigm (41), which uses the predicitve probabilities associated with the different tests. This procedure is over 90% successful, using the Gene-Tox data base, in predicting carcinogenicity. However, the procedure requires that a number of short-term tests be done, and, for the dyes under consideration, was applicable only to R-3.

Because of the present stage of test development, currently short-term tests are usually limited to a confirmatory role for a bioassay, when one is available, in identifying hazards. They may also have a role in the process of prioritizing candidates for testing when a bioassay is not available. In light of the potential broader use of short-term tests in interpreting the results of a bioassay and in elucidating factors in a chemical's mechanism of action, a discussion of the short-term results of the dyes appears to be useful to highlight important considerations in interpreting information on their long-term biological effects.

Many of the chemical and metabolic aspects of the dyes are covered in other chapters. For each specific dye, the results of the short-term tests will be discussed in four categories: mutagenesis; DNA damage/repair; chromosomal aberrations; and transformation (38). However, relevant results are sometimes discussed in more than one class. Because the dyes are not single substances, but mixtures of a certain purity with possible differences relating to the method of manufacture, more than usual emphasis is given to the source of a particular dye used in a test.

IV. COMPARATIVE TOXICOLOGY

A number of long-term animal tests have been done on most of the color additives under consideration; however, not all the test protocols meet current standards. Present standards require that test materials be administered to groups of at least 50 animals, using each sex and two species, at two or more dose levels, the highest of which is a maximum tolerated dose (MTD). The MTD is stipulated as the highest dose of the test material that can be given during a chronic study without altering the animals' normal longevity. Generally, the MTD should not cause more than a 10% weight decrement as compared to the appropriate control groups and should not produce clinical signs of toxicity or pathologic lesions that would shorten the animals' life span. In cases where the MTD cannot be determined, due to lack of toxicity, the convention is to limit the level of test material given to 5% of the diet. Administration of the MTD provides assurance that if no outstanding toxic effect is noted after the test material is administered for the greater part of the animals' life span, usually two years in the case of rats or mice, the null effect was not due to administration of too low a dose. Appropriate control groups with the same number of animals as the experimental groups must be included (42).

Generally, animals are placed on test when six to eight weeks of age. To increase the sensitivity of the test, multigeneration protocols are also employed; in such studies the animal is exposed at all stages of development, including organogenesis and rapid proliferation, presumably more sensitive stages of development. However, the use of this protocol requires an expanded definition of the MTD since a toxic dose and toxic effect for an embryo may be very different from that for an adult organism. The risk assessments used for computing risk have been limited to the results derived from rats and mice, frequently from only one study. Since, for the purposes of this document, weight-of-evidence is not used in determining carcinogenicity, only studies with positive results are used to estimate risk. However, negative studies can play a role in this analysis by serving as information from which a likely range can be determined for estimates of risk. Studies with positive results on the colors under consideration have uniformly used ingestion as the route of exposure, which results in a problem in interpretation since the uses of the dyes being considered by the Panel are, in the main, external uses (although incidental ingestion in lipstick is considered when appropriate). The comparative toxicology part of each chapter notes a number of characteristics for major studies used in the risk assessments. Considerations, such as the questions of interpretation of the results and whether the study reached the MTD, were evaluated. Since the studies are not being used for hazard identification, this analysis is brief. Also included are analyses of the dosing materials and an assessment of the impact of the purity of the material on the results of the long-term test.

V. SKIN PENETRATION STUDIES

As indicated above, the Panel has restricted its attention to drug and cosmetic uses of the colors. For these analyses, an important consideration is the amount of dye that penetrates the skin after application. Skin-painting studies have uniformly been negative for oncogenic effects. Interpreting this, it appears that the skin is not a target organ for any carcinogenic effect. Therefore, a good deal of attention has been paid to the question of absorption of the colors through the skin to estimate systemic exposure for comparison with anticipated systemic exposure after feeding studies.

A series of skin penetration studies, commissioned by CTFA, were done by Dr. T. Franz from the University of Washington (43-46). Since these studies are presently the only adequate data to estimate skin penetrance of the dyes, a synopsis of the experimental technique will be given.

The *in vitro* skin test model consisted of a 1 or 2.5 cm^2 section of human skin mounted in a diffusion cell. The dermal surface of the skin was placed in isotonic saline at pH 7.4 and 37°C. The bathing solution (the receptor phase) was removed and sampled at regular intervals. For some dyes, it was replaced by a Volpo-20 solution to increase dye solubility. The dyes were applied in various concentrations and vehicles, (simulating, to some degree, the composition of commercial products) in volumes of 5, 10, or 25 µl, or as 25 mg talc. The radioactively labeled dyes were left *in situ* for periods of 3 to 7 days, and the absorption of the dye through the skin into the receptor phase was measured with a scintillation spectrometer. The rate used for risk assessment was the steady state rate. Where a steady state was not reached, the maximum rate was used, typically measured at the end of the 3rd day.

The skin sections were obtained from the abdominal skin of deceased hospital patients within 24 hours of their death, and used either immediately or refrigerated for no more than 20 hours. Before mounting in the diffusion cells, the subcutaneous fat tissue and approximately 50% of the dermis was removed by shaving with a scalpel. In a number of cases, the epidermis was also tested (separately from the dermis), in order to investigate the effects of differential retention on tissue permeability.

In interpreting the test results, it should be realized that the model used cadaver skin. Since any postmortem tissue disintegrates with time, it is likely that the skin's integrity as a barrier will be affected. The longer the time since death, the more permeable the skin becomes. Unfortunately, no quantitative data are available on the time dependency of postmortem permeability. Another aspect of the skin model is that artificial canals between the skin surface and the receptor phase have been created by cutting through the sweat and hair ducts. The effect of this artifact has not yet been quantified but will result in raising the observed absorption rate.

Finally, even if the skin model would perfectly simulate *in vivo* physiology, a serious shortcoming is that the amount applied to the diffusion cell did not account for the natural loss of material occurring in practice, *e.g.*, by wiping off excessively applied cosmetics, wearing off or rubbing off, and cleaning. Estimates of this loss of material, *i.e.*, that will not be available for absorption, can be made but are necessarily crude in the absence of adequate test data.

More generally, a recent review article summarizes information on a number of factors important in estimating percutaneous absorption, including the application of *in vitro* to *in vivo* results, site of application and individual variation (47). Information was provided to the Panel that the percent dose absorbed of triclocarbon was significantly different in a static *in vitro* system compared to an *in vitro* continuous flow system (47,48). Since the experimental paradigm used by Franz included changing the bathing solution and altering vehicle to simulate the solubilizing effects of blood flow, the experimental system used was probably more similar to the continuous flow system than a static diffusion cell. Since the data supplied also show that the continuous flow was a fairly good model for *in vivo* human skin for this compound, and that the *in vitro* model also overestimated *in vivo* penetrance for another chemical, paraquat, the Panel determined that the *in vitro* model was not likely to significantly underestimate skin penetrance, although there appears to be significant variation with different chemicals.

On the question of differential absorption as a function of site of application, Dr. Franz stated, in a meeting with the committee on May 30, 1985 (49), that penetration rates through facial skin may be 5-10 times greater than through abdominal skin. The reference supplied by Dr. Franz (50) did not mention penetration through abdominal skin, nor was there any information on females, who are the population especially exposed by color use in cosmetics. In other studies, for a few chemicals tested such as parathion or malathion, the urinary excretion of labelled material as percent of applied dose from jaw or forehead is less than three times higher than in glabous abdominal skin (51). Scrotum and vulval skin absorb more than the forehead (47). Other experiments looking at the absorption of hair dyes under practical conditions of application indicate that an important factor is the surface area of the hair in the region, and it is suggested that the 75-100 times larger surface area of hair on the scalp is the main factor in the relatively low scalp penetration of hair dyes

(0.02%) that penetrate 100 times more in the ventral aspect of the forearm (52). From these considerations, it is likely that penetration rates for the colors under consideration vary in different areas of skin. In order to model absorption through all skin areas, especially for products used all over the body (e.g., bath products, soaps, etc.), the Franz data, conducted on abdominal skin, were multiplied by an overall average absorption value of three.

In summary, the Franz model needs improvement and substantial validation experience under routine conditions to provide information on accuracy and reproducability of the results. Nevertheless, in the absence of currently available established alternatives, the Panel considered the test results usable if interpreted judiciously. The results of the studies are given in the chapter on each dye.

VI. LOW-DOSE EXTRAPOLATION

Because data derived from high dose experiments are being used to estimate risks at low doses, an model must be used to extrapolate to low levels of chemical. One of the extrapolation models used in the CTFA risk assessments (7-10), and used generally by a number of regulatory agencies is the multistage model. Because there are excellent recent reviews (2,3) only a very brief description is given here.

The multistage model calculates the probability of occurrence of a particular tumor type in an individual (P) exposed to a daily dose (d) of a chemical for a lifetime as equal to

$$P = 1 - \exp[-(qo + q_1 d + q_2 d^2 + \ldots)$$

where the q's are parameters estimated from bioassay data. This model can be used to estimate the "upper bound" for low dose risk in a rodent strain under conditions of the test when an upper confidence limit on the linear term q_1 is used in the model (this modification results in the "linearized multistage model"). This procedure does not imply that the data are linear in the observed high-dose range, but conservatively places a linear term in the unobserved low-dose range which is compatable with the 95% confidence limit of the experimental data.

CHAPTER 2. GENERAL ASSUMPTIONS USED IN RISK ASSESSMENT

I. INTRODUCTION

In accord with its charter, the Panel has critically reviewed the risk assessments submitted by CTFA (7-10). The Panel basically agrees with the risk assessment methodology used by CTFA, but questions some of the assumptions used in the analyses. A quantitative risk assessment consists of hazard identification, exposure assessment, dose-response assessment, and risk characterization. In each of the first 3 steps, the assessor will be confronted with uncertainties arising from gaps in scientific knowledge of the mechanisms involved or from the lack of information (1-3,53-56). Such uncertainties can be dealt with by conducting data-generating studies. In most cases that a risk assessment is required, however, no time or resources are available to do such studies. In other situations, the current state-of-the-science is simply not sufficiently far developed to provide adequate answers on intricate and complex issues.

These gaps in information require assumptions to be made in order to estimate risk. Some assumptions are general, some are specific to certain classes of cosmetic products, and some apply only to specific colors. Basically, although the concerns about the estimations of risk by CTFA voiced by CFSAN (6) are real ones that require attention, the procedure used in the CTFA risk assessments is generally consistent with present methodologies used in risk assessment. However, the analysis in this report is more detailed in certain aspects and adds both information to and insight into the judicious utilization of the information contained in those assessments.

CTFA has used a large number of assumptions to cope with the existing uncertainties. Many are explicitly stated, others become apparent only after a careful consideration of CTFA's line of reasoning, or of the methodology used. Since the accuracy of risk estimates is entirely determined by the kind and validity of the underlying assumptions, it seems to the Panel that it is imperative, and of paramount importance, to first highlight and discuss these assumptions prior to doing the actual risk estimation.

It has been the Panel's opinion that this can best be done by means of:

a) concisely and clearly stating the assumptions;

b) providing the Panel's view on the validity of the assumptions;

c) indicating possible options for coping with the uncertainty of concern; and

d) providing an estimate of the quantitative impact of a change in the assumptions on the magnitude of the risk.

It needs emphasis that the assumptions listed in Chapters 2 through 8, although formulated by the Panel, have been implicitly or explicitly made by CTFA. This does not necessarily imply that these assumptions were considered valid by CTFA. Many of the assumptions were made for the explicit purpose of deriving what the CTFA characterized as a conservative risk estimate by overestimating exposure, and were often followed by a discussion reflecting CTFA's awareness that the assumption was erroneous. The Panel's view on these assumptions is expressed in the discussion on their validity and impact on the risk, and in the Risk Characterization sections.

Since filling gaps in knowledge or information may, in certain cases, be done by generating data rather than making assumptions, indications are also given of suitable and feasible studies that may provide the desired information and, thus, reduce the number of necessary assumptions and associated uncertainties.

In this chapter, the general assumptions relevant to all the colors are discussed followed by assumptions relevant to a particular product (e.g., bathing solutions). Those assumptions which are especially relevant to the risk assessment for a particular dye are discussed in the last part of the chapter on each color.

A. Hazard identification

The dyes R-3, R-9, R-19, and O-17 have been found to significantly increase the incidence of tumors in test animals in some assay. Chapters 3 through 8 provide some information on the cancer bioassays and relevant short-term tests. The Panel did not evaluate the weight-of-evidence for carcinogenicity to humans, understanding that it was FDA policy that any chemical shown to be able to induce cancer even in only one strain, gender, and species, at one dose in one experiment, is an animal carcinogen and, thus, a suspect human carcinogen. Accepting this principle does not imply that the Panel members necessarily agree or support that the dyes of concern are indeed human carcinogens. If the weight-of-evidence would have been evaluated, there is the possibility that one or more dyes would not fulfilled criteria (e.g., IARC criteria (57)) to be considered human carcinogens. Accepting the dyes as carcinogens, however, does not eliminate the need for certain assumptions.

B. Exposure assessment

Humans are exposed to the dyes of concern by means of cosmetics, drugs for skin application, and products for personal hygiene. For a proper estimation of risk of cancer, it is necessary to convert exposure (amount administered) into dose (amount absorbed) for oral and skin exposure. Since no human data are available on absorption in gut and through the skin, assumptions need to be made.

To cope with some of the uncertainties and to reduce the need for assumptions, CTFA conducted two surveys on the use of cosmetics and hygiene products, and sponsored in vitro skin absorption tests. The usage surveys included a one week prospective survey of 47 female CTFA employees and their families, and a retrospective survey among 1129 customers of a retail chain run by a major cosmetics producer. Data were available to the Panel for R-3, R-9, R-19, and O-17. Estimation of the rate of the absorption through the skin is based on in vitro testing using postmortem human skin sections as described in Chapter I.V. Interpretation of the results of the usage surveys and the skin tests requires a number of assumptions to be made.

The Panel chose to give two different estimates of exposure. It applied the dye-specific and product-specific assumptions below to different exposure levels, the 90th percentile exposure values, i.e., equal to a value that is less than or equal to that which is expected for 90% of the population affected (understanding that it was a long-standing FDA practice to use this value) and an approximate "reasonable" estimate, based on the anticipated average or mean values.

C. Dose-Response Assessment

For regulatory purposes, the carcinogenic potential of a chemical is usually assessed by testing animals at doses that include at least the MTD (Chapter 1, Section IV). To predict the risk of cancer in humans at the dose levels of concern, which are usually much lower than this dose, the risk assessor has to extrapolate inferences made from results of animal high-dose tests. The Panel used the results of high dose experiments and extrapolated the results to the low doses of concern using a linearized multistage model.

D. Risk Characterization

The CTFA risk estimate, i.e., the probability of developing a tumor in an individual after lifetime exposure to the dose indicated, using the appropriate usage survey, is listed, for the upper 90th percentile and the average (when estimated) usage. This is followed by risk estimates (or unit risks) generated by the Panel, based on consideration of the quantifiable assumptions used in the assessments. Some of the conditions on the estimates are also given, to be used in conjunction with the entire document for proper analysis of the results.

II. GENERAL ASSUMPTIONS USED IN THE CTFA HAZARD IDENTIFICATION

1. Assumption: Any carcinogenic response in an animal test predicts a carcinogenic response in humans.

   Validity: Unknown. It has been shown that all human carcinogens are also animal carcinogens in some assay. However, relatively few of these animal carcinogens have been shown to be carcinogenic in humans. This may reflect either lack of, or deficiencies in, design and implementation of epidemiologic studies. On the other hand, humans may be insensitive, or the animal model may not mirror the human response.

2. Assumption: The carcinogenic potential of a chemical is independent of route of administration and the medium used, i.e., if the dyes are shown to be carcinogenic after oral exposure, it is assumed that skin application would induce cancer as well unless there is evidence to

the contrary.

Validity: Testable by conducting chronic assays by skin application (these assays have been negative for the dyes of concern).

3. Assumption: An animal bioassay is more appropriate for hazard identification if the chemical was tested at or near the MTD. It is assumed that critical metabolic pathways were not overwhelmed and carcinogenic mechanisms are the same regardless of dose.

Validity: Unknown, and at the current state-of-the-science difficult to test.

III. GENERAL ASSUMPTIONS USED IN THE CTFA EXPOSURE ASSESSMENT

A. General Assumptions.

1. Assumption: Orally administered or ingested dyes are absorbed equally well in test animals and man, regardless of the test concentration of the dye and the vehicle used.

Validity: Unknown; it is testable, although rarely done in risk assessments.

Option: Conduct comparative absorption studies in test animals and humans.

Impact: The quantitative impact of the assumption on the risk estimate is unknown, it may result in under or overestimation of the risk.

2. Assumption: In comparing routes of administration, the amount of dye which penetrates the skin will be equally effective as the amount which penetrates the gastrointestinal tract in evoking a carcinogenic response.

Validity: Unknown and testable. There is good evidence that gastrointestinal microflora and skin can activate carcinogens, and by very different mechanisms.

Option: Conduct studies which deliver similar systemic doses by various routes in appropriate animal model systems.

Impact: Depends upon carcinogenic mechanism and agent metabolism, which has not been characterized well.

3. Assumption: For each dye, the exposure is for a lifetime.
   Validity: Obviously invalid and testable.
   Options : Either-
   a) make a more appropriate guess based on practical considerations, and consider males separate from females; or
   b) provide realistic estimates for each product based on surveys among the general population (as opposed to the clientele of these products); or
   c) provide a realistic estimate for all products combined, based on surveys among the general population.

Impact: If exposure started, on the average at age 10, exposure would be for 6/7 of a lifetime, and hence the exposure would be about 6/7 of the CTFA exposure estimate if the relationship between exposure and risk is independent of the age at exposure.

4. Assumption: People use only products that contain the carcinogenic dyes of concern.

Validity: Obviously invalid and testable.

Option: Conduct a survey on actual use of colored and uncolored products in the general population (however, patterns of use can change with time).

Impact: The available data are not sufficient for an accurate impact assessment. In order to reflect the wide variety of products available and the production figures of these dyes compared to all dyes, an arbitrary factor of one-half is used to "correct" the assumption. However, it is clear that more accurate data will probably revise this figure downward. This factor is not likely to underestimate the risk and is more reasonable than 100%.

5. Assumption: People use only products with the highest concentration of the dye.

Validity: Invalid and testable.

Option: Conduct a market survey on the concentration of products.

Impact: Table 9 (7) suggests that the average concentration used is less than 1/4 of the maximum concentration in R-19 commercial products. It is assumed that this is true for the other dyes of concern.

6. Assumption: The relative absorption in humans can be estimated under standardized experimental conditions using 2 to 5 days postmortem abdominal skin specimens.

Validity: Unlikely to be valid, testable. The assumption is based upon the implied claim that a postmortem skin specimen does not differ from live skin with regard to permeability, that skin preparation can be standardized, and that abdominal skin represents other areas of the body as well. As discussed in Chapter 1, this is probably not true. It has been shown that paraquat was absorbed through the skin at least 15 times less _in vivo_ than was predicted _in vitro_.

Options: Conduct rigidly standardized _in vivo_ and _in vitro_ studies using live skin at various sites, in particular including the facial skin and the scalp.

Impact: There are insufficient data available to asssess the quantitative impact of using postmortem skin sections, but the model is very likely to overestimate the true absorption rate. Based on the considerations discussed earlier in the section on the skin penetrance studies, and also considering that a number of the cosmetic products are not used only on the face (_e.g._, bath products, soaps, etc.), the Panel estimates that by using abdominal skin, CTFA probably underestimated the risk by a factor of 3 for products applied to the skin. However, by using the Franz _in vitro_ model, the true absorption may be overestimated substantially. Thus, maintaining a correction factor of 3 seems still a conservative estimate.

7. Assumption: For each dye, the skin absorption rate equals the steady state rate, unless this is not reached after 3 days, in which case twice the maximum rate at that time is used to approximate the absorption rate.

Validity: Seems reasonable for the steady-state, but not for the maximum rate and is testable. Much depends on how well the _in vitro_ skin test reflects reality. It is hard to understand a continuous rising trend in the absorption rate through a skin section 5 or more days postmortem. Since it may be expected that with increasing time postmortem the skin becomes more penetrable to dyes, the absence of a steady state may suggest the presence of an artifact.

Option: Repeat the skin tests with live skin for extended periods of time.

Impact: Since the absence of a steady state after 3 days may reflect a postmortem skin artifact, the assumption that twice the maximum rate represents the true absorption rate probably results in overestimating the exposure. This issue will be dealt with in the dye-specific chapters 3-8.

8. Assumption: The CTFA-sponsored usage frequency surveys are representative of the usage pattern in the population of users of cosmetics and drugs for external use.

Validity: Probably incorrect and testable. The prospective study included CTFA female personnel and their families, while the retrospective study involved clients of a cosmetics retail chain only. Is it not clear whether male clients are also included. It is very likely, in both surveys, that males have been underrepresented, while there is an overrepresentation of frequent users. Further, interviewees of the retrospective survey are likely to be limited to products of one manufacturer only, and, thus, have less variation in products (and, consequently, in dose levels) to choose from.

Options: Conduct surveys among the general population and provide data by age cagegory (e.g., infants, older children, adults, elderly) and gender.

Impact: Table 5 (7) shows that, in general, the prospective study yielded approximately 15% lower usage frequency than did the retrospective study. It is unknown to what extent exposure is overestimated by the non-representativeness of both surveys with regard to the population of product users. In the absence of more appropriate data, the Panel accepts this assumption, appreciating that it overestimates the risk.

9. Assumption: The daily absorbed amount of dye per product used

equals:

$$a \times b \times c$$

where a = the amount of dye in the product per application

b = the frequency of application (following the usage survey

c = the percent absorbed per day of applied amount.

Validity: Unknown, it can be challenged.

Option: Conduct _in vivo_ and _in vitro_ (with live skin) studies and measure the amount available for absorption (rather than the amount applied), the amount applied per cm^2, the surface covered by the product, for varying frequencies of application per day with soluble and insoluble dyes.

Impact: Since the value of c depends on many variables, such as the equilibrium between penetration rate and tissue retention, the amount of dye lost by wiping or wearing off (indicating a difference between the amount applied and the amount available for absorption), the thickness of the skin layer of product, the diffusion rate of dye in this layer, etc., there may be either an under- or over-estimation of exposure, by using the above approximation. Typically, cosmetics are regularly removed by cleaning or wearing off. If the cosmetic is not immediately re-applied, the absorption will probably drop because the steady-state absorption rate, reached _in vitro_ after three days, will probably not be reached. This consideration is especially germane to the more insoluble dyes which reach the steady-state absorption rate much more slowly than the others. Then, the use of the steady-state rate in the above equation would overestimate exposure. However, a model which is based on one application in 2-3 days, when the real-life situation includes more frequent applications, will underestimate exposure because frequent application will cause the average concentration of the thin dye layer directly in contact with the skin to have a higher average concentration (it doesn't become as depleted and as dependent on diffusion from the more dye-rich layers above to replenish it in a short time as opposed to 2-3 days). This factor is, again, especially significant for the insoluble dyes since the diffusion rate (and replenishment) will be slow. Since no information is available to support and/or quantify the above considerations, the Panel used the CTFA equation.

10. Assumption: For each dye the total exposure is the sum of exposures to all products containing the dye of concern.

Validity: A reasonable and testable assumption.

Option: Test mixtures rather than single dyes.

Impact: Although unlikely, it is possible that there is dye-dye interaction or that there is some change in skin penetration as a function of the number of dyes being present. Interaction with the various kinds of vehicles may lead to either underestimation or overestimation. However, the overall impact is not likely to be substantial.

11. Assumption: The amount of consumer product per application made is 5-10 mg/cm^2.

Validity: Unknown, but testable assumption. In the CTFA risk assessments, values have been listed without reference and lacking information about distribution.

Option: Establish a data base on the amounts of dye used per application and the skin area exposed, through a general survey of the population.

Impact: Since there is no information, this assumption cannot be assessed. It may over or underestimate exposure.

12. Assumption: Differences in the vehicles used in the skin absorption studies are not likely to result in changes in the absorption of more than 10-30%.

Validity: Unknown but testable. There may be little similarity between the vehicle used in the absorption studies and the actual test product, e.g., nail polish uses vehicles which ensure fast evaporation to form a tough water- (and serum-) insoluble film.

Option: Expand the skin studies to include vehicles more similar to those used in consumer products.

Impact: Without data, no accurate estimate can be made of the effect of the test vehicle. There are no data to support the estimate of a 10-30% variation, nor is there any information on the direction of the difference. In the example of nail polish given above, the film would probably prevent absorption through the skin.

13. Assumption: In an appropriate vehicle, there is no difference between a color in a formulation used as a primary dye or in a lake form.

Validity: Unknown, but testable.

Option: Conduct skin absorption studies using both lakes and primary dyes.

Impact: There are no data available for assessing the impact. Since the lakes are made to restrict the water solubility of the dye, the use of lakes would probably result in less absorption through the skin.

14. Assumption: That the major constituent of the dye is of primary toxicological concern and can be modeled by the skin absorption test.

Validity: Reasonable and testable.

Option: Repeat skin absorption studies and account for impurities, both for differential absorption and carcinogenic "potency".

Impact: No data available for an accurate impact assessment. From analysis of the actual impurities present in certified lots of dye, the major impurities of concern are the subsidiary colors (present at a maximum of 5%) and residual starting materials (present at a maximum of 0.5%). The subsidiary colors are so similar to the major dye component that it is unlikely that there are significant differences between skin penetrance and potency of the subsidiary color and the major component, which leaves the risk assessment unaltered. For the residual starting materials, from a toxicological point of view, they are unlikely to be more than five times as potent and ten times as capable of penetrating the skin as the major dye component. If this is so, their maximal effect can be calculated as follows.

For ingestion, one mg of commercial dye has, maximally, 5 µg of starting material, with a maximal potency of 5 times the original dye or 25 µg dye-equivalents. In the gut, 995 µg of the actual dye + 25 µg dye-equivalents, the total absorbed 50%, yields a value of 510 dye-equivalents producing the toxic effect. The value is 500 for the principal component considered by itself, leading to a correction factor of 500/510 (approximately one) for each dye-equivalent when related to the toxic effect to account for the effect of contaminants.

For the skin, at 1% absorption for the principal component (and subsidiary colors) and 10% for the contaminant, one mg of dye results in 9.95 µg dye-equivalents + 0.5 µg dye-equivalents times a potency of 5 or 2.5, which is 12.45. The value is 10.00 for the principal component considered by itself, leading to a correction factor of 12.45/10.00 X 500/510 (to relate to the gut absorption data) which is approximately 1.22.

Thus the effect of significant impurities (starting matreials and subsidiary colors) is likely to be less than a factor of 1.2 times the risk estimate derived from considering only the major component.

B. Product-Specific Assumptions

1. Assumption: For hair cosmetics, 2% of the applied dye reaches the skin, i.e. the ratio of hair area to skin area is assumed to be 50:1.

Validity: The data provided to support this: the total surface of hair is 75-100 times the surface of the scalp; for risk assessment purposes it is conservatively assumed that the hair surface is 50 times the skin surface. The approach seems reasonable if the total hair surface is indeed 75-100 times the skin surface, which may be an underestimation for females.

Option: Compile data on hair length, diameter and density.

Impact: No data available for an accurate estimation. If the estimate is too low, the risk estimate is proportionally too high. Since the hair/skin surface ratio may already be too low, further lowering to a value of 50 is an unnecessary application of a safety factor of about 75/50 = 1.5 to 100/50 = 2.0. A proper correction factor for CTFA exposure estimates, therefore, seems to be 1/1.75 or approximately 0.6.

2. Assumption: For nail products, 1% of the applied dye reaches the skin or the cuticle.

Validity: Reasonable and testable, but it still does not account for vehicle volatility.

Option: Conduct a test of nail products under realistic conditions.

Impact: Since nail polish is intended to dry up to an insoluble film almost immediately after application, the penetration rate of dyes from such products is virtually zero. The solvents in nail polish are highly volatile, and it is very unlikely that under this condition a measurable dye absorption would occur in the very brief period of application. Absorption of dye from nail creams and lotions would theoretically be possible. The test model, however, did not accommodate for nails as the area of application. Given the low frequency use of this product (7-10) and, in view of the above discussion, assuming a zero absorption of dyes from nail products is, in practice, not an underestimation of the risk.

3. Assumption: For bathwater products, 2% of the applied dye reaches the skin. It is assumed that a layer of 1 mm of water, equaling 1.8 liter of water, would cover the body to form the source from which dye can be absorbed; this is 1.8% of an assumed 100 liters of bathwater.

Validity: Reasonable and probably testable.

Option: Conduct [illegible] _in vivo_ study of animals immersed in a dye solution.

Impact: Unknown due to lack of data, but not likely to be significant.

4. Assumption: Products used for a short period only (wash-off products) have an absorption of 50% of that of products in continuous use, regardless of how short the actual exposure was.

Validity: Seems incorrect and is testable.

Option: Repeat skin test focused on amount of dye retained in the skin during various short periods of time.

Impact: The information provided by the skin tests suggests that the absorption for wash-off products is far less than 50% of that for products with continuous use, and hence that the exposure is considerably overestimated. An absorption rate of 25% of the rate for products used continuously seems more realistic. More information is required for a more accurate quantification of the assumption.

5. Assumption: For products other than wash-off products it is assumed that the amount applied equals the amount available for absorption.

Validity: Incorrect and testable. It is likely that in most applications of cosmetics they are applied in excess and they wear or are rubbed off. Therefore the amount left for absorption is less than the amount applied. The overestimate of exposure is related to the amount removed, i.e., not available for absorption.

Option: Conduct studies focused on measuring the proportion of applied product that is either removed by wiping off or by contact with materials other than skin (e.g., clothes, skin).

Impact: The amount of dye available for absorption is hard to quantitate. It seems reasonable, however, to assume 50% loss for products other than wash-off products. It is probably correct to not apply this correction factor to products in a water-alcohol vehicle.

IV. GENERAL ASSUMPTIONS USED IN THE CTFA DOSE-RESPONSE ASSESSMENT

1. Assumption: In the long-term studies by feeding in rodents, there is 100% absorption of the dyes.

Validity: Unknown and is testable. Feces may be colored which suggests that some dye was not absorbed. However, because of processes such as biliary excretion, elimination of the compound in the feces does not indicate lack of absorption. Some of the benzidine azo dyes, which also showed colored feces, demonstrated low absorption when given by the oral route. A likely absorption range is 25-75%.

Option: Conduct absorption studies for oral administration.

Impact: Unknown, and may lead to an underestimate of risk for externally used products. If only 50% of the carcinogen is absorbed from the feed, then tumors are produced by 1/2 of the administered dose. Hence, risks for dyes absorbed through the skin should be multiplied by 2. No correction is needed for internal exposure from swallowed lip products, if the proportion absorbed by the oral route is similar in humans and rodents.

2. Assumption: If a color is carcinogenic in humans, the risk of cancer for a lifetime exposure in humans is equal to the risk for a lifetime (approximately two years) exposure in rodents for equal daily doses on a body weight basis (mg/kg body weight/day).

Validity: Probably not true. Hoel et al. (58), suggested the use of dosage units (i.e., a metameter) of mg/m^2 body surface area-day on the basis of the acute toxicity of anticancer drugs in humans (59). Crump et al. (60), using a data base derived from the NTP bioassays for over 200 chemicals, concluded that the dosage measurement giving the closest correlation between species was mg/kg body weight-day. However, use of relations such as these has lead to concern. It has been noted that -

> " It does not appear safe to generalize concerning rates of unknown metabolic reactions. Many exceptions could be found to the apparent tendency of intrinsic rate to decrease with increasing body size: Quite different qualitative pathways may dominate in different species and toxicity may sometimes correlate with the concentration of an active intermediate that represents only a minor elimination pathway" (61).

Different rates of metabolism, especially for agents which require metabolism for activation, would alter the response. There is no direct evidence to assess the relative carcinogenic potency of these colors between humans and rodents. However, for 15 carcinogenic agents, the relative potencies between humans and the most sensitive rodent data were generally within a factor of twenty, either high or low, when dose was measured in terms of mg/kg body weight (53). To generalize, for an individual chemical, the risk estimate calculated could be low or high by a factor of 100. Quantitatively, extrapolation on a surface area basis would multiply the CTFA risk estimates by approximately 7 for those based on rats and 12 for mice.

Option: Would require epidemiological data. Since anticipated cancer risks are small, an extremely large study would be required. Exposure would be difficult to measure and is not practical. Alternatively, pharmacokinetic analyses in combination with knowledge of the carcinogenic metabolites may be adequate to define a good metameter.

Impact: Unknown, could be substantial in either direction.

3. Assumption: For extrapolation purposes for these dyes, a woman is considered to have a lifetime average body weight of 53 kg.

Validity: Probably valid for the general female population, unknown for the population of cosmetic users.

Options: Conduct a survey of weights among the product users.

Impact: A value of 60 kg as a lifetime average weight of the general population (including males) is commonly used by the FDA. Since the products are likely to be used predominantly by females, with males unlikely to be exposed to products having significant dye concentrations (aftershave lotion, bath soap, etc. have very low dye concentrations), it seems reasonable to accept 53 kg for the risk calculation.

4. Assumption: The linearized multistage model provides an upper bound on low dose risk estimates provided we are in the convex portion of the dose-response curve.

Validity: Probably provides an upper bound on low dose risk estimates for the rodent species (62). The appropriate model to choose for "best" estimates is unknown. Various models may fit the experimental data equally well, but may differ considerably at the lower doses. Even if the multistage model is appropriate, whether or not a linear term is included makes a considerable difference at the lower doses. If a linear term is present, the "best estimate" may be within a factor of two of the upper bound estimate. If a linear term is not present however, the "best" estimate may be several orders of magnitude below the upper bound estimate. Thus, even restricting estimation to the multistage model can not establish a "best" estimate because the high dose experimental data can not establish the presence or absence of low-dose linearity. Therefore, "best" estimates should not be attempted as was done by CTFA even for the rodent species. In the light of uncertainty as to carcinogenic mechanism, the use of a model incorporating low-dose linearity is consistent with a recent suggestion by the OSTP carcinogen document (2).

Option: Other linearized models could be used, but they are not likely to vary much from the linearized multistage model estimates.

Impact: If these colors act to add to carcinogenic processes already existing in humans, then low dose linearity is expected. The choice of the model then offers no additional safety asssurance and does not impact on the risk estimates. If the colors act by independent processes to produce cancer and low dose linearity does not result, the upper bound estimates may be higher than actual risk by several orders of magnitude.

5. Assumption: The most sensitive animal tumor data (species-strain-sex-tissue or organ site) are the most appropriate indicator for human sensitivity and are generally used to estimate risk.

Validity: No direct evidence that this would or would not be a reasonable representation of very sensitive human subpopulations.

Impact: Unknown, could be substantial. The selection of the best animal model to predict cancer incidence in the "most sensitive" human subpopulations is seldom known and would probably vary with the carcinogen being considered. The use of this assumption is in accord with a recent suggestion included in the OSTP carcinogen document (2).

V. RISK CHARACTERIZATION

The assumptions and the discussion of the associated uncertainties can be summarized as follows.

A. The Panel's Assumptions Used in Hazard Identification

The assumptions used in the CTFA risk assessments have been accepted by the Panel, because there seem to be no alternatives with higher degree of validity for the uncertainties involved and because some are consistent with what the Panel understands is FDA policy. Uncertainties may range from no risk to humans to underestimation of the risk. In general, it is believed that the assumptions accepted are conservative, i.e., that they are more likely to overestimate rather than underestimate the true risk. The Panel's assumptions in this category are:

1. All 6 dyes of concern are animal carcinogens in some assay and, thus, suspect human carcinogens. The Panel has made no evaluation of the weight-of-evidence for human carcinogenicity from the animal test results.
2. Orally administered or ingested dyes are equally well absorbed in

animals and humans, regardless of the test concentration of the dye and of the vehicle used. This assumption agrees with that of CTFA's.

3. The Panel used data from positive studies for risk assessment, assuming high-dose studies were appropriate for low-dose extrapolation, in accord with the CTFA risk assessments.

B. The Panel's Assumptions Used in Exposure Assessment.

General Assumptions

1. The dyes were assumed to be equally absorbed in rodents and man.

2. Dye which penetrates the skin was considered to be as effective in evoking a carcinogenic response as if ingested.

3. For each dye, exposure is for 60 years, in contrast to CTFA's use of 70 years. Also assuming the risk is not influenced by age at exposure, the associated correction factor is 6/7.

4. An arbitrary value was used to reflect the fact that cosmetic products do contain other dyes than those of concern (or no dyes at all). Compared to the CTFA estimate, a correction factor of 0.5 will be used.

5. Based on data for R-19 only, the average concentration of all dyes in commercial products was assumed to be 25% of the highest concentration allowed. Compared to the CTFA estimate, a correction factor of 0.25 will be used.

6. The *in vivo* skin model used for the skin absorption studies is accepted for assessing the exposure to absorbed dye. However, the model is likely to overestimate the risk. For products applied to the facial skin, the model may underestimate the real absorption rate by a factor of 3.

7. In interpreting the results of the *in vitro* study on the absorption rates over time, it is assumed that the true absorption rate equals the steady state rate. Where the test did not reveal a steady state, twice the maximum rate at the end of 3 days may approximate the true absorption rate. This assumption agrees with CTFA's.

8. Both types of CTFA surveys of the frequency of the use of dye containing products overestimate the frequency among the general population. Since the Panel is considering the risk of cosmetic users, the CTFA estimate of the exposure, as derived from the prospective

usage survey, was used. However, the value is an overestimation for the population.

9. The absorbed amount of dye per day can be estimated by multiplying the amount of dye per day available for absorption by an absorption rate constant, as estimated from the in vitro tests. This agrees with CTFA's assumption, although the Panel believes that this may well be a conservative estimate. There is insufficient information, however, to calculate a better estimate.

10. For each dye, the total exposure is the sum of exposures to all products containing the same dye. This assumption agrees with CTFA's and is probably close to the best estimate.

11. The amount of dye-containing product per application equals 5-10 mg/cm^2, which is in agreement with CTFA's estimate. There is no information available for assessing the best estimate of the amount per application.

12. With the exception of nail products, the composition of the vehicle used in the commercial products does not affect the absorption rate assessed with the in vitro skin model, which accords with CTFA's assumption. There is insufficient information to generate a best estimate of the absorption rate for each kind of commercial vehicle. Assumptions on nail products are discussed in the next section.

13. In an appropriate vehicle, there is no difference in absorption rate between a primary dye and its lake, which is in agreement with CTFA's assumption. However, there is no information to generate the best estimate for primary dye or lake-specific formulations.

14. To address the question of contaminants, it is assumed, based upon consideration of the structure and toxicity of actual impurities found in certified lots, that for the subsidiary colors that they are likely to be so chemically similar that the skin penetrance rates are not likely to be significantly different from the principal constituent (which doesn't affect the risk estimate), while the other substances of concern, residual starting materials, can be calculated as having, at most, an effect of multiplying the risk by 1.2. CTFA's estimate of the exposure is thus corrected with a factor of 1.2.

Product-Specific Assumptions

1. The absorption rate for hair cosmetics is 1.2% of the applied amount, which requires a correction factor of 0.6.

2. No absorption occurs from dyes in nail products. CTFA assumes 1% of the applied amount will penetrate the skin.

3. For bathwater products, 2% of the applied amount reaches the skin, in agreement with CTFA.

4. For wash-off products (including bathwater products) an absorption of 25% is assumed, rather than the 50% assumed by CTFA (CTFA also excluded bathwater products from this consideration), which requires a correction factor of 2.

5. For products other than wash-off products, an absorption of 50% is assumed rather than the 100% assumed by CTFA, which requires a correction factor of 2.

C. The Panel's Assumptions Used in Dose-Response Assessment

1. In test animals, 50% of orally administered dyes are absorbed from oral studies and the carcinogenic response is caused by this absorbed portion. The associated correction factor is 2.

2. On a mg/kg body weight basis, dose levels used in animal tests are assumed to have the same quantitative effect on the cancer incidence in humans, which is in agreement with CTFA's assumption. There is insufficient information for assessing the best estimate of the correct dose unit for use in extrapolating animal risk to human risk of cancer.

3. An average body weight of 53 kg. for woman is assumed, as done by CTFA.

4. The linearized multistage model is assumed to reflect the true relation between dose and response. This agrees with CTFA's estimate. The linearized multistage model may offer no added protection if we are in the convex portion of the dose-response curve and low-dose linearity is appropriate or may overestimate the risk by several orders of magnitude if low-dose linearity is not present.

5. The most sensitive animal tumor data are used to extrapolate risk from animal data to humans, however risk estimates based on other species are given for comparison.

D. Conclusion on the Total Impact of Assumptions on the Risk Estimate

In the dye-specific chapters, the product- and dye-specific assumptions were applied to the usage data contained in the CTFA risk assessments to adapt the exposure values, e.g., if absorption through the use of nail polish for a dye was assumed to contribute 0.0002 ug/day to the total exposure, the use of the correction factor (Chapter 2.III.B2) of zero results in this amount becoming zero. The Panel used these assumptions with survey estimates of 90th percentile exposure (the Risk/90 values) and average and "reasonable" estimates of exposure (Risk/Rea) to derive the revised risk estimates.

The quantitative impacts of the general assumptions which are quantifiable concerning exposure and dose-response are below. For skin absorption, the correction factor equals:

(6/7 X 0.5 X 0.25 X 3 X 1.2 X 2) = 0.8 times the CTFA estimate

For incidental ingestion of lip products, a number of factors relevant only to skin absorption or not relevant to lipstick products drop out:

(6/7) = 6/7 times the CTFA estimate

At low dose levels, the risk of cancer, as computed with the linearized multistage risk model, is directly proportional to the dose levels (see Assumption 2.IV.3 and Ref 2). The above correction factors are multiplied by the appropriate risk estimates based on the adjusted exposure estimates calculated as indicated above.

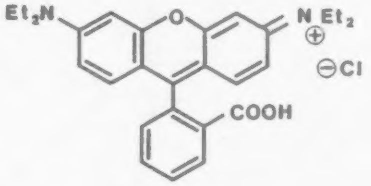
To place this in perspective, the Panel recognizes that the correction factor of 0.8 for skin absorption is inconsequential compared to the uncertainties in the assumptions that are difficult to quantify. The correction factor for skin absorption does not mean that the risk estimate is precise within 20% of the actual human risk. What this figure represents is that, for the various quantifiable assumptions, underestimates and overestimates of risk in the CTFA estimates basically cancel out. It should not be forgotten that less than ten of 19 identifiable assumptions are even approximately quantifiable, some only with fairly arbitrary factors. Also, sometimes, figures are used for absorbed dose with three or more significant figures. The use of this many figures does not imply precision; it is merely a mathematical tool to avoid cumulative rounding errors. It must also be understood that these assumptions, and the risk assessments that derive from them, are directed at estimating the effects from exposure to a single chemical only. They do not include possible effects of exposure to multiple chemicals such as co-carcinogenesis, promotion, synergism or antagonism.

The Panel, following prudent public health policy, has tended to accept assumptions which are likely to overestimate rather than underestimate risk in the cases difficult to quantify and feels that the human risk in the following risk estimates is more likely to be over- rather than underestimated.

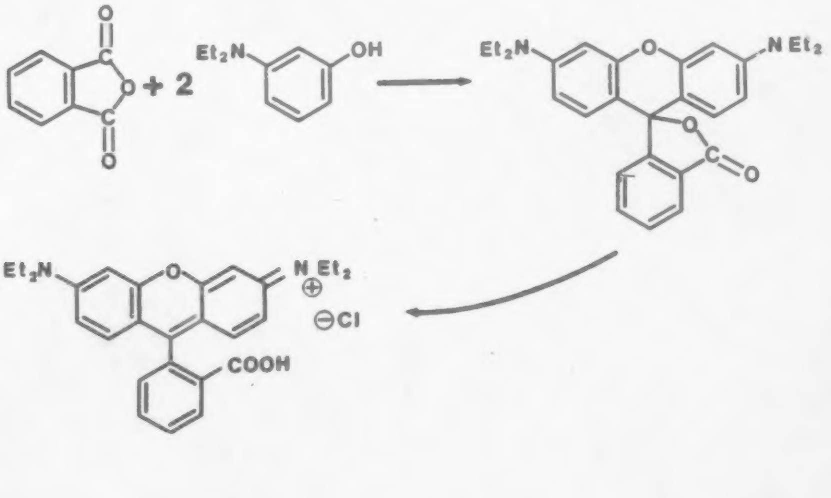
CHAPTER 3. D&C RED NO. 19 (R-19)

I. CHEMISTRY

D&C Red No. 19 (CI 45170) (R-19) (CAS 81-88-9) is the water-soluble xanthene dye 9-(2-carboxyphenyl)-3,6-bis(diethylamino)-xanthylium chloride (FDA also terms it the 3-ethochloride of 9-o-carboxyphenyl-6-diethylamino-3-ethylimido-3-isoxanthene). Its common name is Rhodamine B and its structure is shown below (12,63). The color is closely related to R-37 which is the stearate rather than the chloride.



R-19 is synthesized from the condensation of phthalic anhydride and 3-diethylaminophenol to produce a colorless lactone intermediate, which is saponified and acidified to produce the hydrochloride pigment (12). The synthetic pathway is shown below.



FDA certification requires that each color lot meet the following specifications (13):

Volatile matter, not more than 5.0 percent.
Water-insoluble matter, not more than 1.0 percent.
Ether extracts (from acid solution), not more than 0.5 percent.
Dimethyl-m-aminophenol, not more than 0.2 percent.
Chlorides and sulfates of sodium, not more than 1.0 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 92.0 percent.

As indicated in Chapter 1, Section I, the methods suggested for certification are not rigorous, and do not fully characterize the purity of the color, as percent of color additive, or the amounts and variety of impurities that may be present including subsidiary colors, side reactions during synthesis and possible degradation products. The reduction of the dye with titanium trichloride determines "% color", often confused with "% purity" and is by no means a measure of actual purity.

A FDA report (12) describes impurities likely to be present as phthalic anhydride, phthalic acid, diethyl-m-aminophenol, resorcinol, o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid, and triethylrhodamine. Side reaction and degradation products were listed as possibly present but in low concentrations. The Environ Report (11) states that possible impurities include the starting materials, phthalic anhydride and diethyl-m-aminophenol, and the intermediate o-(2-hydroxy-4-diethylaminobenzoyl) benzoic acid, as well as the subsidiary color, triethylrhodamine. In addition, simple aromatic amines that could be extracted in ether are conceivable impurities. Commercial dye lots were shown to contain triethylrhodamine and o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid. Investigators in Japan (20), using an HPLC method with reverse phase chromatography and detection at 230 nm showed the absence of starting materials in commercial dyes, but the presence of peaks described as subsidiary colors. Some of the impurities are of toxicological significance since it has been shown that impurities after separation by TLC are mutagenic by the Ames test (64).

If the FDA specifications are followed and the methods for the determination are sufficiently rigorous for screening purposes, then the levels of these organic impurities when totaled should not exceed 2-4% by weight. The likelihood that this total level of impurities is confined to a single compound is low. Most of the impurities seem to be composed of the subsidiary color, triethylrhodamine (12).

II. SHORT-TERM TESTS

A. Mutagenicity

A number of studies found R-19 gave no response in the bacterial Ames tests, using tester strain of *Salmonella typhimurium* TA98 in a sample from FDA (65), in TA98 or TA1535 using a sample from a major textile firm (66) or, in a sample from Merck Chemical Co. over a wide dose range in TA98 or TA100 (67) (a report that the dye was inactive in a number of other strains was considered problematical because the dye was inhibitory to the bacteria under the conditions used in the assay [68]). Other authors, however, reported that dye supplied by the Sigma Chemical Co. (64) or in a rhodamine dye tablet (used to trace water flow) (69) was mutagenic in TA98, 100 and 1537, as was a dye lake in TA98, TA1537 and TA1538 (70). The key to understanding these data was provided by the observations that the positive response seemed to be a result of impurities in the dye. When another dye source, with less impurities, was used (64) or the impurity separated by fractionation (64), the dye was not mutagenic. In higher organisms, the dye did not induce gene conversion in yeast (71), although there was a weak mutagenic effect when the dye (without fractionation) was added to food for Drosophila (72). From these studies it appears that the mutagenic activity of this dye is contained in impurities.

B. DNA Damage/Repair

A *rec* test in *E. coli* was negative (73), while positive induction of DNA breaks in the *in vitro* Chinese Hamster Ovary cells (CHO) assay was suggested to be related to the lethality of Rhodamine B at the doses used or impurities (64). As an index of recombinative activity, the dye did not induce gene conversion in yeast (71). In CHO cells, DNA damage does occur (74), but at doses with significant cell lethality (75). The lethality is not surprising since the dye has been shown to be phototoxic at lower doses to cultured human skin cells (76). The CHO studies were conducted using "gold" lights (75) which remove the ultraviolet and blue portion of the spectrum. However, the photoactivation spectrum for the toxic effect of the dye is well into the visible region (76), which would not be removed by "gold" fluorescent illumination. It appears that the toxicity of the dye is an important factor in its ability to damage DNA.

C. Chromosomal Damage

Chromosomal aberrations were not found in a human cell line at concentrations up to 10^{-4}M (77), or in onion root tip or broad bean in culture (78). However, clastogenic effects were found in Muntjac chromosomes (79), and CHO cells (74,80). No induction of bone marrow sister chromatid exchanges (SCE) in the mouse was found at high doses (81).

For the study with Muntjac cells, the dye was obtained from Sigma Chemical Co., a source which was shown to contain mutagenic impurities (64). It was not purified before use. In one of the studies using CHO cells (80), the cellular toxicity of the dye was not reported, but, if it is similar to that seen in the study by Douglas et al. (74), it was appreciable at the doses reported to induce an effect. In the other study using CHO cells (74), the dye was fractionated before use. However a significant effect is seen at a dose approximately at the LC_{50} for the culture (75), under conditions of "gold" illumination, which is discussed above. Although the dye has clastogenic effects, they could be a result either of an impurity in the dye or of dye toxicity.

D. Transformation

No assays.

E. Significance

The results suggest that the observed genetic toxicity of R-19 may be a result of non-colored impurities in commercial preparations or may be an indication of dye toxicity, especially phototoxicity. Rhodamine B is phototoxic, and should be handled properly when assayed for genetic toxicity.

From the information available in the literature, it is not clear what are the stability characteristics of fractionated dye. Fractionated dye appears to be non-mutagenic and only damages DNA in doses high enough to induce cell lethality.

III. COMPARATIVE TOXICOLOGY

A. Negative Studies

1. Rat- R-19 was fed to Wistar rats (5 male and 5 female) at 4% of the diet for 2 years. No toxic or oncogenic effect was noted (82).

   R-19 was fed to 21 male and female Wistar rats at 0.13% of the diet for 7 months and then at 0.2% in a lifetime study. No significant effects were noted (83).

   R-19 was also fed at 0.008, 0.025 and 0.15% of the diet to groups of 25 male and 25 female SD rats at each level for 104 weeks. Growth suppression was noted in male and female rats at 0.025% and 0.15% levels. Male rats at the 0.008% level also had lower body weights from about the 40th week. There were increases in the thyroid weights and thyroid/body weight ratios (84).

   R-19 was fed to 25 male and 25 female Charles River rats at 0.004% of the diet for 26 months and no adverse effects other than pink coloration of the eyes were noted (85).

   R-19 was fed to Long-Evans rats at 0, 0.04, 0.4 and 4 mg/kg in the diet in a three-generation study, each generation involving 10 males and 20 females at each dose level. No oncogenic effect was noted (86).

   R-19 was fed to CD rats (60 males and 60 females/group in Fo and 70 males and 70 females at F_1) in diets containing 0, 0.002, 0.005 and 0.02%. In this two-generation study that continued for 30 months, body weights were somewhat lower in high-dose females (87).

2. Dog- R-19 was fed to 3 male and 3 female beagle dogs per group at 0.008%, 0.0325% and 0.1% of the diet for 2 years. No oncogenic effect was noted (88).

3. Skin painting- In mice, 0.1 ml of a 1% solution of R-19 was painted twice weekly on the backs of 50 male and 50 female ICR Swiss-Webster mice for 18 months. No oncogenic effect was noted, even in skin (89).

B. Positive Studies

1. Rats- In CD rats, a multi-generational study similar in protocol and numbers to the one that found no significant effect at 0.02% used 0 and 0.075 % levels of R-19 in which the animals were dosed for 132 weeks with *in utero* exposure (90). Animals on the 0.075% dose had a significant reduction in body weight and a significant increase in follicular cell tumors of the thyroid in treated males.

TABLE 1 INDUCTION OF THYROID FOLLICULAR TUMORS IN CD RATS

		Adenomas (%)	Carcinomas (%)
Controls	M	2/57 (7.0)	1/57 (3.5)
	F	2/57 (7.0)	0/57 (0.0)
0.075%	M	12/56 (21.4)	5/56 (8.9)
	F	5/56 (8.9)	1/55 (1.8)

2. Mouse- CD-1 mice (60 animals/sex/group) were dosed at levels of 0, 0.005, 0.02 and 0.1% in the diet for 24 months. Hepatocellular carcinomas were increased in females (91).

TABLE 2 INDUCTION OF HEPATOCELLULAR TUMORS IN CD-1 MICE

Level (in wt. %)	Males		Females	
	Carcinoma (%)	Adenoma or carcinoma (%)	Carcinoma (%)	Adenoma or carcinoma (%)
0 (control)	9/119 (7.6)	17/119 (14.3)	0/115 (0.0)	4/115 (3.5)
0.005	8/60 (13.3)	14/60 (23.3)	2/60 (3.3)	6/60 (10.0)
0.020	5/59 (8.5)	12/59 (20.3)	5/60 (8.3)	8/60 (13.3)
0.100	9/59 (15.3)	15/59 (21.5)	14/60 (23.3)	19/60 (31.7)

C. Interpretation

1. Interpretation of the rat study

a. Toxicology - Rats fed R-19 at 0.075% had moderate weight depression but no effect on survival was seen. Females had more severe weight depression. Toxic lesions in the potential target sites, thyroid and parathyroid glands, were not seen.

b. Pathology - Increased incidence of thyroid follicular tumors (adenomas and carcinomas) was found in 0.075% males (17/56) as compared with controls (3/57). Five of the dosed males had carcinomas while one control male had thyroid follicular carcinoma. Goiter was not reported.

In females, 6/55 dosed rats had thyroid follicular tumors and 2/57 were found in control females. Parathyroid tumors were reported in 9/48 dosed males and 1/44 control males. Few chemicals, if any, cause these parathyroid tumors. Since it is easy to misdiagnose parathyroid hyperplasia (due to renal disease) as neoplasia, these lesions should be reviewed histologically.

c. Conclusion - This study showed R-19 led to tumors in male rats. More severe body weight depression was noted in females which did not have induced tumors. Goiter was not noted.

The R-19 was obtained from Sun Chemical Corporation as a FDA certified lot, with a stated "purity" of 92%, lot AA-4989. No data were included on the further characterization of the purity of the color additive or the presence of impurities.

A supplementary report submitted by Dr. Slattery for the petitioner showed that lot AA-4989 of the dye contained 1.58% triethylrhodamine, expressed as the ratio of triethylrhodamine to R-19 at 554 nm, and about 0.4% other colored impurities, expressed as the ratio of impurities to R-19 at 554 nm (21). This report did not mention non-colored impurities. The FDA's Division of Food and Color Additives laboratory reported the analysis of lot AA-4989 as 90.3% color, 2.8% volatiles, 0.09% insolubles, and 2.3% triethylrhodamine (12).

Studies were performed on stability of the dye in diets at all dose levels, the homogeneity of the dye in the feed, and verification of the dye content of prepared diets. Simple screening methods were used, and were judged adequate for quality assurance purposes.

The studies seemed to be well controlled, but lack definitive information on the purity of the dye and the levels of impurities that may be present. Supplemental submissions (21) and FDA's Division of Foods and Color Additives Laboratories reports (12) provide data that generally indicate that levels of organic impurities were between 2-4%.

From the point of view of chemical purity of the dosing material, these studies were performed in an acceptable manner except for the lack of sufficient data on the purity of the dye and the presence of impurities. Subsequent analysis of the dyes used in the bioassays showed the presence of 1.6-2.3% triethylrhodamine and the presence of unspecified "other" impurities as separated by TLC (21). FDA also reported data related to the purity and presence of impurities in this lot and showed that the principal contaminant, triethylrhodamine, was present at 2.3%

2. Interpretation of the mouse study

a. Toxicology - The feeding of diets containing R-19 at a level of 0.1% did not produce effects on body weight gain or mortality. Mild toxic liver lesions were found in mice.

b. Pathology - Increased incidences of liver tumors were found in both sexes. Dosed males (0.1%) had an incidence of 15/59 as compared with 17/119 in the control males while 0.1% dosed females had an incidence of 19/60 versus 4/115 in the control females. More than 50% of the liver tumors in dosed mice of both sexes were malignant.

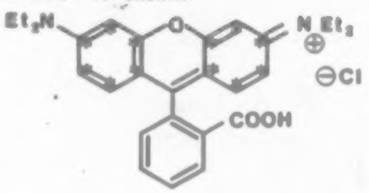
c. Conclusion - This study showed feeding R-19 led to liver tumors in female mice. Since no effect was found on body weight gain or survival of both sexes, it is possible that the mice could have tolerated higher doses of R-19. The mild toxic liver lesions in male mice would also support this position.

The chemical analysis of the dosing material used, and the conclusions of the analysis about the mouse study were identical to the rat study that was analyzed since the the studies were done together.

IV. SKIN PENETRATION STUDIES

Since the question before the Panel involved external uses of the color, especially in cosmetics, skin penetration studies were evaluated as part of extrapolating the results of the toxicological findings to practical conditions of use and exposure.

The Franz *in vitro* studies in human abdominal skin (43) used ^{14}C labelled R-19 obtained from Amersham Corporation as "side rings-U-(^{14}C)" Rhodamine B, having a specific activity of 38 mCi/mmol (79 μCi/mg). The presumed location of label is shown:



TLC assays for radiochemical purity, reported by Amersham, using two solvent systems indicated 95 and 96% purity. TLC assays were also performed by Dr. Slattery from the University of Washington (21). Three TLC bands were separated, scraped, eluted and counted. The results showed 92.6% Rhodamine B, 5.48% triethylrhodamine, and 1.96% "other" determined from the radioactivity found in eluted bands. When quantitation of the bands was based on absorption at 554 nm, the results showed 97.1% of Rhodamine B, 2.0% triethylrhodamine and 0.9% "other". Non-colored impurities would not be detected by the latter method. Specific activities calculated on a total weight basis were 85.3 and 81.7 µCi/mg as compared to 79 µCi/mg reported by the supplier, Amersham.

Radioactive dye was prepared in aqueous formulations of different pH, as well as in alcohol, oils, emulsions, and talc. Doses varied from 0.001% in aqueous formulations to 0.5% in talc. Appropriate amounts of ^{14}C were applied to approximately 1 cm^2 of human abdominal skin mounted in the Franz cell with receptor saline solution.

Recoveries from aqueous buffers and emulsions were good with significant retention in the epidermis. Recoveries from oils were also good with significant amounts removed with the first wash. No recoveries were performed with talc.

Results showed a 2% pH-related penetration of dye in aqueous buffers with smaller penetration in emulsions, oils and talc. The radiochemical purity was well defined in the supplementary report by Dr. Slattery. As discussed in the general section on the skin penetration studies, the effect of differences in skin penetrance in different skin regions cannot be quantitated with present information. There are still questions as to impurities present and the nature of the ^{14}C component that was found in the receptor cells, but these questions are largely academic and would have a relatively small impact on risk assessment when using the assumptions discussed.

V. SPECIFIC ASSUMPTIONS USED IN RISK ASSESSMENT

1. Assumption: Emulsions are assumed to be absorbed at a rate of 1%/day of the amount applied, which is the rate seen for aqueous

solutions. The observed rate of 0.24% may be too low since:

(a) it was unclear whether the observed rate reached the steady state; and

(b) emulsions contain the soluble dye rather than the lake.

Validity: Probably invalid, it is easily testable.

Option: Conduct new studies on emulsions for an extended period of time, and include live skin specimens.

Impact: Figure 3 (43) of the skin study shows that the steady state was reached after approximately 60 hours. The argument that emulsions contain the dye rather than the lake is irrelevant, since the test was performed with the dye (43, appendix B, page 3). Moreover, since it is already questionable whether 3-5 days postmortem skin would retain its original integrity, the assumption of a rate of 1%/day implies a safety factor of 4.

2. Assumption: Since a steady state was not reached with mineral oil as a vehicle, an absorption rate of twice the maximum rate after 3 days is assumed for oil-based products.

Validity: Unlikely to be correct, it is testable.

Options:

(a) Conduct in vivo tests in humans and suitable animals;

(b) Repeat in vitro test for extended periods of time with live skin.

Impact: Using twice the absorption rate of mineral oil (0.5%/day) for products based on castor oil is incorrect since the latter rapidly reached a steady state rate of 0.04%. The assumption implies the application of a safety factor of 12.5. As to mineral oil in particular and all other vehicles in general, the main issue is whether postmortem skin is a good model for live skin, which appears to depend on the dye and other factors. It seems more reasonable to assume that postmortem skin becomes increasingly penetrable with time than it is to assume that the skin's integrity is retained throughout the test. If postmortem artifacts prevent mineral-oil based dyes from reaching the steady state, risk estimates based on the test results are considerably too high. A reasonable estimate of the mineral oil absorption rate, given the results in postmortem skin, should be assumed to equal the observed maximum rate of 0.25% (rounded). For castor oil products, no reasons have been found to depart from the observed steady state rate of 0.04%.

3. Assumption: The absorption rate for aqueous products is assumed to be 1%/day of the applied amount, except for those products that need adjustment (see product-specific assumptions, chapter 2, section III.B).

Validity: Seems correct based on the in vitro data.

Impact: The data provided (Table 7 of Ref. 7) show a range of steady state absorption rates of 0.82 to 1.03%/day, where 1.03% refers to a 0.001% aqueous solution at pH=8. Since 0.001% is the maximum concentration of the commercial products and not a median or average, this assumption is one that will probably overestimate the rate.

4. Assumption: The absorption rate for talc products is 0.002%/day of the amount applied.

Validity: Seems corrrect based on the in vitro data.

Impact: The above rate is a steady state rate achieved as soon as 2 hours after application. Thus, the effect of further deterioration of the skin with time is minimal.

VI. RISK CHARACTERIZATION

A. Summary of Dye-Specific Assumptions (Chapter 3.V)

1. The absorption rate of dyes in emulsions equals 0.25% per day of the amount applied to the skin. This estimate is in contrast to CTFA's assumed 1% absorption rate.
2. For products based on mineral oil the dye absorption rate equals less than 0.25% per day of the applied amount, as compared to CTFA's 0.5%. With regard to products based on castor oil, the absorption rate equals 0.04%, as compared to CTFA's assumed 0.5%.
3. For aqueous products, except for those that need adjustment (see Chapter 2.III.B), the absorption rate per day equals 1%, which is in agreement with CTFA's assumption.

4. For talc products, 0.002%/day is absorbed from the amount applied, which is in agreement with CTFA's assumption.

B. Summary of Product-Specific Assumptions (Chapter 2.III.B)

1. For hair cosmetics, the CTFA-estimate that 2% of the applied amount of dye reaches the skin is an overestimation, requiring a correction factor of 0.6.
2. For nail products, the absorption of dyes is assumed to be zero, as compared to CTFA's assumption that 1% of the dye applied is available for absorption, to which specific absorption rates are then to be applied.
3. For bathwater products, 2% of the applied dye reaches the skin, where it is available for absorption, in agreement with CTFA's assumption.
4. For "wash-off" products, regardless how short the exposure time, the absorption rate is 25% of that of products used continuously, compared to 50% assumed by CTFA.
5. For products other than "wash-off" products, it is assumed that not more than 50% of the amount applied is available for absorption, as compared to CTFA's assumption that 100% of the applied amount is available.

C. CTFA Risk Estimates

1. From the BIO/DYNAMICS Study in CD-1 Mice.

The risk was slightly higher using liver tumors (adenoma or carcinoma) rather than hepatocellular carcinoma only. The estimates of the upper confidence limit on low-dose risk from the linearized model (but not the tumor incidences) were comparable in males and females and, therefore, combined. Using the exposure estimates based on the prospective usage study, CTFA (4) calculated an upper bound on lifetime risk to humans from external use

$= \quad 1.3 \times 10^{-7}$ for 0.062 μg/kg-day absorbed.

2. From the BIO/DYNAMICS studies in Charles River CD rats

The risk was somewhat higher using thyroid follicular cell tumors (adenoma or carcinoma) rather than carcinoma only. Results in males and females were similar and therefore combined. Using the exposure estimates based on the prospective usage study, CTFA (4) calculated an upper bound on lifetime risk to humans from external use

= 2.7 x 10^{-7} for 0.062 µg/kg-day absorbed.

D. Revised Risk Estimates

Application of the product- and dye-specific assumptions above 2 categories of assumptions to the usage data (Tables 8 and 9, Ref. 7) results in a total absorbed amount of dye of:

0.42 µg/day as an average of the prospective usage survey;

1.62 µg/day as the upper 90th percentile of the prospective survey, as compared to CTFA's estimates of 0.85 µg/day and 3.27 µg/day, respectively.

0.53 µg/day as an average of the retrospective usage survey;

1.87 µg/day as the upper 90th percentile of the retrospective survey, as compared to CTFA's estimates of 1.06 µg/day and 3.77 µg/day, respectively.

As discussed earlier, the prospective survey is likely to be less biased than the retrospective study. The doses pertaining to the prospective study will, therefore, be used for calculating adjusted risk estimates. At the low dose levels resulting from use of cosmetics, using the linearized multistage extrapolation model, the dose-response curve is straight linear. This means that the risk of cancer is directly proportional to the dose. The following estimates are based on 53 kg as a lifetime weight average for women, and include the correction factor of 0.8 to adjust for the Panel's view on the quantifiable general assumptions (Chapter 2.III.A and 2.V).

	Risk(CTFA/90)	Risk(CTFA/Avg)	Risk/90	Risk/Rea
Rat	2.7 X 10^{-7}	7.1 X 10^{-8}	1.1 X 10^{-7}	2.8 X 10^{-8}
Mouse	1.3 X 10^{-7}	3.4 X 10^{-8}	0.5 X 10^{-7}	1.3 X 10^{-8}

Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

Risk(CTFA/Avg) is the CTFA risk estimate at "average" estimates of exposure.

Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.

The above risk estimates are based on the reasonable estimates of exposure, whenever the Panel believed that it was possible to make such an estimate. In situations where available data would allow for a choice between "degrees of reasonable estimate", the Panel consistently selected the estimate associated with the higher risk.

If the dose conversion (metameter) from rodents to humans is made on a surface area basis rather than on a body weight basis (mg/m^2-day rather than mg/kg-day) the risk estimates would be raised by a factor of 7 for the estimate based on rat data and 12 for the estimate based on mice. The use of an upper 95% confidence limit for the linearized multistage model utilized in the low dose extrapolation probably leads to an overestimate of risk for rodents. Assuming equal susceptibility for rodents and humans, and also using the most tumor-sensitive site and species, in conjunction with conservative estimates of exposure, are likely to lead to an overestimate of risks for humans.

VII. CONCLUSION

Studies have been conducted on TLC separated dyes that showed that the impurities (UV-absorbing) were mutagenic by the Ames test while the purified dye fraction had little indication of mutagenicity. The levels of these impurities may have an impact on R-19 carcinogenicity. However, because of the relatively low concentration of these impurities, their presence is not likely to alter the risk assessment calculations of risk of the entire dye by a significant degree.

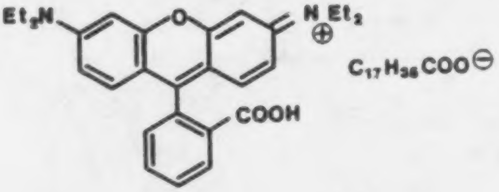
Although the risk of R-19 is low, the impurities may be responsible for some of its toxicity. It is recommended therefore that the impurities be removed before it is used. It should be possible to develop simple techniques which are cost-effective, and inclusion of a purification step as a criteria for certification, removing those impurities which have significant mutagenic action, would probably reduce an already small risk.

Finally, the dye has been shown to be phototoxic. Conditions of its use and the possibility of effects as a result of light exposure should be considered.

CHAPTER 4- D&C RED NO. 37 (R-37)

I. CHEMISTRY

D&C Red No. 37 (CAS 6373-07-5) (CI 45170:1) (R-37) is an alcohol soluble xanthene dye 9-(2-carboxyphenyl)-3,6-bis(diethylamino)-xanthylium octadecanoate (FDA also terms it the 3-ethostearate of 9-o-carboxyphenyl-6-diethylamino-3-ethylimido-3-isoxanthene). Its common name is rhodamine B stearate and its structure is shown below (12,92). It is structurally related to R-19 which was previously discussed.



R-37 is synthesized from R-19 by treatment with ammonium hydroxide and stearic acid (92).

FDA certification requires that each color lot meet the following specifications (13):

Volatile matter, not more than 2.0 percent.
Water-insoluble matter, not more than 1.0 percent.
Sulfated ash, not more than 3.0 percent.
Matter insoluble in benzene, not more than 0.5 percent.
Dimethyl-m-aminophenol, not more than 0.2 percent.
Stearic acid (not part of the dye), not more than 50.0 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 50.0 percent.

Therefore, approximately half the molecular weight is taken up by non-colored stearate anion. As discussed in the general section, the methods of certification are not rigorous and do not fully characterize the purity of the color, as percent of color additive, or the amounts and variety of impurities that may be present, including subsidiary colors, side reactions during synthesis and possible degradation products.

A FDA report (12) describes impurities likely to be present as phthalic anhydride, phthalic acid, diethyl-m-aminophenol, stearic acid, fatty acids related to stearic acid, o-(2-hydroxy-4-diethylaminobenzoyl) benzoic acid, and triethylrhodamine. A variety of possible side reaction and degradation products were listed as possibly present, but in low concentrations. The Environ report (11) does not address R-37, but any impurities are expected to be similar to those reported for R-19. Commercial dye lots were shown to contain triethylrhodamine, stearic acid and o-(2-hydroxy-4-diethylaminobenzoyl)benzoic acid. Other investigators analyzed lots of dye from Japanese sources by an HPLC method, using reverse phase chromatography and detection at 230 nm and reported the absence of starting materials but the presence of 6-7 peaks believed to be subsidiary colors (20). Some of the impurities are likely to be of toxicological significance since it has been shown that impurities separated from the closely related dye R-19 by TLC are mutagenic by the Ames test (64).

If the FDA specifications are followed and the methods for the determination are sufficiently rigorous for screening purposes, then the levels of these organic impurities, less stearic acid when totaled, should not exceed 2-4% by weight. The likelihood that this total level of impurities is confined to a single starting material is low. Most of the impurities seem to be confined to the subsidiary color, triethylrhodamine (12).

II. SHORT-TERM TESTS

A. Mutagenicity

In addition to the information on R-19, R-37 was found not to be mutagenic, with or without activation, in TA98, TA100, TA1535 and TA1537 (68).

B. Other

No additional information.

C. Significance

R-37 is negative in a mutagenic assay in a laboratory that also found R-19 to be negative. There is no reason to believe that the color will be less contaminated with impurities than the parent R-19, except that the presence of the stearic acid will dilute the contaminant.

III. COMPARATIVE TOXICOLOGY

No long-term animal assays have been performed with this color additive. The presence of the stearate is not likely to affect the toxicological effects of the color once absorbed, except by simple dilution of the dye concentration. It is not clear whether the moiety will decrease gastrointestinal absorption because of decreased water solubility, or increase it as a result of ion-pairing effects.

IV. SKIN PENETRATION STUDIES

No skin penetration studies have been performed with this color additive. It is not clear whether the moiety will decrease skin penetrance because of decreased water solubility, or increase it as a result of ion-pairing effects.

V. SPECIFIC ASSUMPTIONS USED IN RISK ASSESSMENT

1. Assumption: The experience with R-19 can be used to predict the risk from R-37.

Validity: Reasonable and testable. Although it can be assumed that once absorbed, the stearate salt would be metabolized to R-19, the issue of concern is absorption. R-37 might be expected to be more slowly absorbed because of its larger molecular weight and its decreased water solubility. In addition, because of the stearate moiety, certified lots of R-37 only contain about 50% color by weight compared to more than 92% color for R-19. However, there is a question that ion-pairing effects might alter the absorption rate. Therefore it is prudent to assume, in the absence of specific information, that the response will be similar to that seen for R-19.

Option: Conduct tests on the toxicity and skin penetrance of R-37.

Impact: The direction and degree of absorption and risk change is not clear. The dilution by the stearic acid will reduce risk by a factor of 2 for the same weight of dye. However, if twice as much dye (the same amount of "color") is used in applications, this factor will disappear. There is no information on usage of R-37. However, use of R-19 data will probably significantly overestimate the exposure.

VI. RISK CHARACTERIZATION

A. Summary of Dye-Specific Assumption (Chapter 4.V.1)

1. The experience with R-19 is used to predict the risk from R-37. On a weight basis, the color moiety (the R-19 component) of the R-37 molecule is approximately 50% of the R-37 molecule. Since it is expected that carcinogenicity is not induced by the stearate, the risk of cancer from R-37 is 0.5 times the risk from R-19 for the same weight of the substance.

B. CTFA Risk Estimates

CTFA does not estimate risk from this dye.

C. Unit Risk Estimates

Since no dye-specific information appears to be available with regard to usage frequency, in vitro skin absorption, and commercial formulation, and because R-37 differs from R-19 only in the added stearate moiety, R-19 data on toxicology and skin absorption have been accepted as likely to represent R-37. It is, therefore, appropriate to correct the risk estimates to be derived for R-37 by 0.8 (similar to R-19) for the general assumptions and, additionally, with a factor of 0.5 for dilution of color with the stearate moiety in the R-37 molecule. The chance of underestimating risk from R-37 is likely to be low because of the very low production of R-37 compared to R-19.

It must be appreciated that there is no exposure information (and little toxicological information) for this color, and the risk estimate is based on simple extrapolation from a chemically related dye. Thus, the nature of this risk estimate is different from those calculated for R-19, O-17, R-9 and R-3. The risk estimate of 1.3 X 10^{-7} (one-half of the risk based on rat data for R-19) is actually a unit risk, i.e. a risk calculated on the basis of a particular unit of exposure, i.e., for an external exposure of 0.062 µg/day to R-19-type dyes. There is no information on actual human exposure, other than the production of the dye which is much less than the production of R-19.

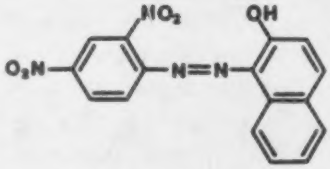
VII. CONCLUSION

In the few systems tested, there is no evidence that this dye is genetically toxic. It is reasonable to assume that R-37 has the same toxicological effects as R-19, except that the unit risk is divided by two for an equal weight of dye. The unit risk estimates should be used to calculate absolute risks as soon as usage data become available, with absorption studies of dye-specific absorption to adjust the risk.

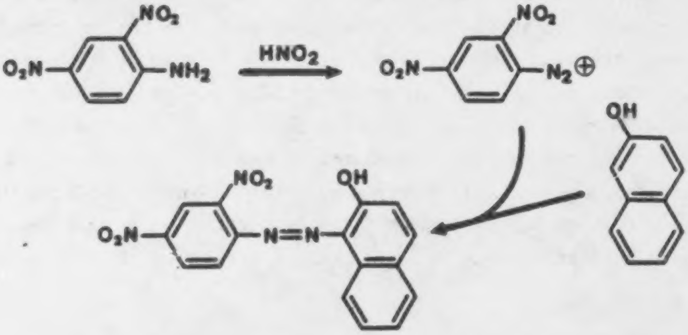
CHAPTER 5. D&C ORANGE NO. 17 (O-17)

I. CHEMISTRY

D & C Orange No. 17 (CAS 3468-63-1) (CI 12075) (O-17) is a water-insoluble monoazo pigment 1-[(2,4-dinitrophenyl)azo]-2-naphthalenol (also termed 1-(2,4-dinitrophenylazo)-2-naphthalenol by the FDA). Its common trade name is Permanent Orange and its structure is shown below (93).



O-17 is synthesized by the condensation of the diazonium salt of 2,4-dinitrobenzeneamine (2,4-dinitroaniline) with 2-naphthalenol (2-naphthol, beta-naphthol). The synthetic pathway is shown below (14).



FDA certification requires that each color lot meet the following specifications (13)

Volatile matter, not more than 5.0 percent.
Sulfated ash, not more than 1.0 percent.
Matter insoluble in toluene, not more than 1.5 percent.
2,4-dinitroaniline, not more than 0.2 percent.
Beta-naphthol, not more than 0.2 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 90.0 percent.

As discussed in the general section, the methods suggested for certification are not rigorous, and do not fully characterize the purity of the color, as percent of color additive, or the amounts and variety of impurities that may be present including subsidiary colors, side reactions during synthesis and possible degradation products.

An HPLC method for the determination of the two starting materials was developed by an FDA scientist, Dr. Alan Scher. His method showed much higher levels of 2,4-dinitrobenzeneamine and 2-naphthalenol than by the FDA certified cellulose column chromatography method, primarily because the HPLC method solubilized the insoluble pigment and released more impurities trapped in the crystal structure of the insoluble pigment (15). The results from the HPLC analyses imply a higher level of starting materials in FDA certified lots than reported by the standard certification method.

A FDA report (14) describes the impurities likely to be present as 2-naphthalenol (<0.2%), 2,4-dinitrobenzeneamine (<0.05%), 4-[(2,4-dinitrophenyl)azo]-1-naphthalenol (<0.05%), 2-[(2,4-dinitrophenyl)azo]-1-naphthalenol (<0.005%), 1-[(4-nitrophenyl)azo]-2-naphthalenol (<0.05%), and possibly a trace of 1-[(2,6-dinitrophenyl)azo]-2-naphthalenol. Other possible side reaction and degradation products were also listed as possibly present but at low trace concentrations. The Environ report (11) states that the most likely impurities are the starting materials 2,4-dinitrobenzeneamine and 2-naphthalenol, although small quantities of ether-extractable nitroaromatics are conceivable. Commercial pigment lots were shown to contain the two starting materials and the first three subsidiary colors listed above. The starting material 2,4-dinitrobenzeneamine, a nitroaromatic amine has been shown to be mutagenic in the Ames test, with and without activation (94).

II. SHORT-TERM TESTS

A. Mutagenicity

This dye is mutagenic in TA98, 100, 1535, 1537, and 1538 with or without S9 activation (71), with increased activity with microsomal activation except for TA1535. It is also mutagenic whether the source is FDA (65), a major textile firm (66), in rouge and lipstick (65,68) or from other sources (95). Microsomal activation has been shown to increase (71) or inhibit (65-67,95) the response, the difference in reaction to the microsomal mix perhaps reflecting impurities.

In the forward mutation assay using the TK locus in L5178Y mouse lymphoma cells, O-17, from 0.65 to 5 mg/ml, is inactive (96) with and without metabolic activation.

B. Other

There were no data for DNA damage/repair, chromosomal damage or transformation.

C. Significance

This dye is a mutagen in bacteria, although not in the one mammalian system tested. There may also be contaminants in the preparation which may be responsible for the difference in the effects of microsomal activation. However, the reduction product 2,4-dinitrobenzeneamine is mutagenic and doesn't require activation (94), possibly because the bacteria possess nitroreductases. This azo reduction to a nitrobenzeneamine may be the source of much of the activity. Whatever the source, it is clearly an agent which directly damages the genome.

III. COMPARATIVE TOXICOLOGY

A. Negative Studies

1. Mouse - CD-1 mice (60 animals/sex/group) were dosed with 0.025, 0.25 and 1.0 % O-17 in the diet for 23-25 months. There was an increase in hepatocellular neoplasms in males, but the increase did not appear significant, compared to controls (97).

2. Rat - O-17 was given at 0.025, 0.1 and 1% of the diet to groups of 25 male and 25 female CD Charles River rats for 104 weeks. Some growth suppression was noted at the higher level. Liver weights were increased in higher dose females. Neoplastic nodules of the liver and hepatocellular carcinomas were increased in females at the 1% dose level although not significantly (85).

3. Dog - 0-17 was fed to 3 male and 3 female beagle dogs per group at 0.025, 0.125% or 1% of the diet for 2 years. In general the treated dogs showed lower body weight gains than controls. However, no significant pathological effects were noted (88).

4. Skin Painting Studies - In mice, 0.1 ml of a 1% solution of 0-17 was painted on the skins of 50 male and 50 female ICR Swiss-Webster mice twice weekly for 18 months. No oncogenic effect was noted even on the skin (89).

0.1 ml of a 1% solution of 0-17 was applied weekly to the skins of 50 male and 50 female CF-1 Carworth mice for up to 26 months. There was no oncogenic effect even on the skin (98).

B. Positive Studies

1. Rat - In another long-term study at Biodynamics, 0-17 was given at 1% of the diet initially to Fo (60 per sex/group) and then the F1 generation (70/sex/group) of Charles River rats for 26-30 months. Mortality of treated rats was increased over that of controls in the second year. Male rats had an 18% depression in body weight. Pericholangitis increased in treated male rats killed at 12 months. A similar effect was noted in female rats but at terminal sacrifice the incidence of this lesion was similar in control and treated rats. There was an increase in hepatocellular adenomas in treated female rats at the terminal sacrifice (18 in treated vs 1 in controls) (99).

C. Interpretation

1. Interpretation - Rats

a. Toxicology - There was no weight depression in males fed 1% 0-17 until 26-50 weeks. The chemical produced no weight depression in females. No effect on survival was found. Toxic hepatic lesions were seen in females but not in males.

b. Pathology - Liver tumors (hepatocellular adenoma or carcinoma) were found in increased incidence in females (21/59) fed 1% 0-17 as compared with controls (3/52). The majority of these rats had hepatocellular adenomas while only 4 rats had carcinomas in the 1% group (one animal had both an adenoma and a carcinoma). Two carcinomas, however, were found in female controls. Mammary fibroadenomas were found in increased multiplicity and total numbers in 1% female rats but the incidence of these tumors was not significantly increased (34/59) as compared with controls (28/51).

c. Conclusion - The liver tumors and toxic liver lesions were found only in female rats. Based on lack of changes in body weight gain and survival these rats may have tolerated higher doses of O-17. The same effect may have been seen on the mammary tumors. However, the study is adequate.

O-17 was supplied by CTFA as FDA certified lot No. AA 6260 and listed as "97% pure". No data were included on the further characterization of the purity of the color additive or the presence of impurities. This certified FDA lot should contain less than 0.2% of the starting materials, however, analysis of this lot showed 0.29% 2,4-dinitrobenzeneamine and 0.70% 2-naphthalenol when analyzed by the HPLC method (15).

Stability and pigment-diet homogeneity studies were performed on the diets at all concentrations. With one brief excursion, at one dose level for a two week period, dose verification was within quality assurance guidelines.

The study seems to be well controlled but lacks definitive information on the purity of the pigment and the levels of impurities that may be present. 2,4-Dinitrobenzeneamine, a known contaminant, is mutagenic. As noted above, the O-17 is mutagenic in bacteria. It is not soluble in water, so there is some question whether the color was absorbed totally in the gut of the rats, but this has not been established.

2. Interpretation of the mouse study

a. Toxicology - Feeding of dietary levels of 1% of O-17 produced no depression in body weight gain. In the males, however, there was an effect of dose on survival. The cause of this increased mortality was not reported but toxic lesions were induced such as pigmentation in various tissues and myocarditis.

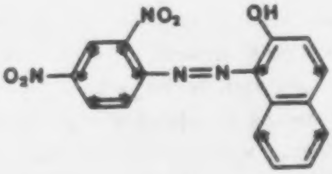
b. Pathology - There was an equivocal increase in liver tumors in high dose male mice.

c. Conclusions: Increased mortality and toxic lesions were found in male mice, but this does not provide definitive evidence for carcinogenicity in mice.

The chemical analysis of the dye lot was similar to the rat study since they were done together.

IV. SKIN PENETRATION STUDIES

The study by Franz (44) used ^{14}C-D & C Orange No. 17 obtained from Amersham, UK as 2,4-dinitro [U-^{14}C]phenylazo-2-[1,4,5,8-(^{14}C)]-naphthalenol with a reported specific activity of 5.6 mCi/mmol. The ^{14}C label is distributed as shown:



The supplier stated that the synthesis method used insures an equal contribution of the specific activity from each labeled part of the molecule. Amersham supplied data indicating that the radiochemical purity was 95% and 96% determined by TLC separation in two solvent systems. The presence of subsidiary colors or the identification of the remaining 4-5% of the radioactivity was not stated.

Dose formulations were prepared in oils and cream blusher at 0.6% color and in talc at 5% color. Approximately 1.5 million disintegrations-per-minute (DPM) of color was applied in oils, 4.7 million in cream blusher, and 38 million in talc. Volpo 20 was used in the receptor cell to aid solubilization of the pigment.

Recoveries of 80-90% were seen in oil formulations and 40-50% in cream blusher. Recoveries were not addressed in the talc studies. Most of the dose was removed with toluene skin washes, although ^{14}C was found in all skin preparations. Counting efficiencies were not stated.

This study used pigment formulations of defined radiochemical purity; however the nature of the 4-5% impurity was not addressed. The question of solubility of the pigment and receptor solution was adequately discussed.

The rate of penetration through the skin was low.

These studies by Dr. Franz were generally performed well. The radiochemical purity of the pigment and its labelling pattern were described, however, 4-5% of the radioactivity was not accounted for and could be present as a radioactive starting material or as side reaction products.

The rate of penetration of the pigment through the skin was low. A concern can be raised that if the radioactive impurity was all 2,4-dinitrobenzeneamine (4-5% of the ^{14}C) it might be preferentially absorbed by the skin. Since, however, skin absorption of ^{14}C was less than 0.03% of the amount applied/day in liquid media and less than 0.001% of the amount applied/day in talc formulations, it is unlikely that this impurity would have a significant impact on risk assessment calculations because of the generally small amount of material that penetrates.

The question of relative penetration for facial skin is discussed in the general section on skin absorption studies (Chapter 1.V).

V. SPECIFIC ASSUMPTIONS USED IN RISK ASSESSMENT

1. Assumption: For creams and oils the absorption rate is 0.01%/day.

Validity: Unknown but testable. However, for insoluble materials, the interpretation of these rates is not simple.

Option: Conduct a live skin test for extended periods of time.

Impact: The skin test revealed rates of 0.003 to 0.007% of applied amount/24 hours, implying an overestimation of the absorption by a factor of 2. However, the real factor is unknown because it is not clear whether the above rates refer to a maximum rate or a steady state rate.

2. Assumption: The absorption rate for O-17 in talc is 0.001% per day of the amount applied.

Validity: Probably correct and testable.

Options: Repeat in vitro skin studies with live skin models.

Impact: CTFA mentioned 0.001% absorption in its text, but printed 0.00009% in Table 6 (8), which referenced Table 2 in Franz's report (44). The latter reference uses the values 0.001%. The laboratory data sheets are difficult to interpret. 0.001% will be used.

3. Assumption: The use of Volpo 20 in the receptor of the Franz cell will not significantly alter the skin penetration.

Validity: Probably valid and testable. _In vivo_ there are a number of factors, such as protein binding in blood flowing through the capillary bed, which would remove the dye when it passed through the skin "solubilizing" the color, which was the reason for using the Volpo 20.

Option: Conduct parallel studies _in vivo_ and _in vitro_ using saline and 6% Volpo 20.

Impact: Use of Volpo 20 may result in higher observed skin penetrance rates, however the effect on the exposure is not likely to be significant since total penetrance using Volpo 20 was extremely low.

VI. RISK CHARACTERIZATION

A. Summary of Dye-Specific Assumptions (Chapter 5.V)

1. For creams and oils, the skin absorption rate is 0.005% per day of the amount applied, which is half the rate assumed by CTFA.
2. For talc formulations, the skin absorption rate is 0.001% per day of the amount applied, in agreement with the rate assumed by CTFA.
3. The low skin absorption rate of O-17 is unlikely to be caused by the insolubility of the dye in the receptor phase. Replacing the usual saline receptor phase by one containing Volpo 20 did not result in increased dye penetration.

B. Summary of Product-Specific Assumptions (Chapter 2.III.B)

1. For nail products, the absorption of dyes is assumed to be zero, as compared to CTFA's assumption that no dye will be absorbed through the nail but that during application 1% of the dye may reach the skin or cuticle, where it will be available for absorption at the usual 1% rate.
2. For products other than "wash-off" products, it is assumed that not

more than 50% of the amount applied will stay available for absorption, as compared to CTFA's assumption that applied amount equals available amount.

C. CTFA Risk Estimates

1. From the BIO/DYNAMICS Study in CD-1 Mice.

The risk estimate was slightly higher using liver tumors (adenoma or carcinoma) rather than hepatocellular carcinoma only. Males were more sensitive than females. Using the exposure estimates based upon the prospective usage study, CTFA (8) calculated an upper bound on individual risk for males

= 0.7×10^{-10} for 0.00039 µg/kg-day absorbed.

2. From the BIO/DYNAMICS Studies in Charles River CD Rats.

The risk estimate was based on liver tumors in females. Data from two studies were combined to provide two dose levels plus controls. Uisng the exposure estimates based on the prospective usage study, CTFA (8) calculated an upper bound on individual risk in females

= 2.1×10^{-10} for 0.00039 µg/kg-day absorbed.

D. Revised Risk Estimates

Information on the usage frequency indicates that O-17 is present in 4 different groups of products (Table 5 and 7, Ref.8). Application of the product- and dye-specific assumptions to these usage data results in a total absorbed amount of dye per day of

0.00189 µg/day as an average of the prospective survey;

0.00635 µg/day as the upper 90th percentile of the prospective survey;

0.00367 µg/day as an average of the retrospective survey; and

0.007 µg/day as the upper 90th percentile of the retrospective survey.

The comparable amounts calculated according to the CTFA assumptions are the upper 90th percentiles 0.0208 µg/day (prospective survey) and 0.01542 µg/day (retrospective survey). As discussed earlier, it is believed that the prospective survey yielded less biased usage frequencies. Calculation of the resulting cancer risk estimates will, therefore, be based on dose estimates based on this survey. At these very low dose levels the dose-response curve is linear, meaning that the risk is directly proportional to the dose. The following estimates are based on 53 kg as a lifetime weight average for women, and include the correction factor of 0.8 to adjust for the Panel's view on the quantifiable general assumptions (Chapter 2.III.A and 2.V).

	Risk(CTFA/90)*	Risk/90	Risk/Rea
Rat	2.1×10^{-10}	5.1×10^{-11}	1.5×10^{-11}
Mouse	0.7×10^{-10}	1.7×10^{-11}	0.5×10^{-11}

*- Note that CTFA does not give an average exposure estimate for 0-17.

Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.

The above risk estimates are based on the reasonable estimates of exposure, whenever the Panel believed that it was possible to make such an estimate. In situations where available data would allow for a choice between "degrees of reasonable estimate", the Panel consistently selected the estimate associated with the higher risk.

If the dose conversion (metameter) from rodents to humans is made on a surface area basis rather than on a body weight basis (mg/m^2-day rather than mg/kg-day) the risk estimates would be raised by a factor of 7 for the estimate based on rat data and 12 for the estimate based on mice. The use of an upper 95% confidence limit for the linearized multistage model utilized in the low dose extrapolation probably leads to an overestimate of risk for rodents. Assuming equal susceptibility for rodents and humans, and also using the most tumor-sensitive site and species, in conjunction with conservative estimates of exposure, are likely to lead to an overestimate of risks for humans.

VII. CONCLUSION

The animal studies were properly controlled except for a lack of data on the purity of the pigment (subsidiary color) or on the levels of impurities, at least one (2,4-dinitrobenzeneamine) of which is a strong mutagen. If this pigment was certified by FDA according to FDA specifications and the cellulose column chromatography method, the level of free amine should not exceed 0.2%. However, FDA's Dr. Alan Scher showed that the level of free amine was 0.29% in this lot using the HPLC method. The HPLC method, with its more vigorous solubilization of the insoluble pigment would result in the detection of higher levels of impurities than would be reported by the certification method.

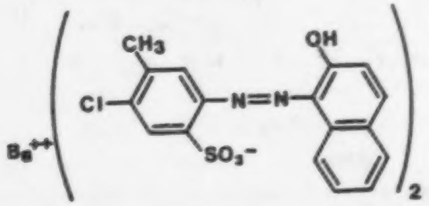
The level of impurities may have an impact on risk assessment only if the degree of potency of the impurities is substantially greater than the pigment. Based on the strong mutagenicity of 0-17 without activation in several strains, the mutagenicity of the azo reduction product and the reported mutagenicity of 2,4-dinitrobenzeneamine with or without activation, it is unlikely that the carcinogenic "potency" differs from the parent compound by several orders of magnitude, and the general assumption concerning impurities is even more likely.

It is important not to ignore the definite mutagenicity of the agent and its metabolite in bacteria. Because the chemical is only slightly soluble, one can speculate that the extent of absorption by the gut may be small, however, the role of intestinal bacterial enzyme activity, such as azo reductase on the azo bond, in producing soluble products should not be ignored. Possible slow absorption may be a factor in the weak carcinogenic response, and the risk assessment figures should be used cautiously with this genetically toxic agent.

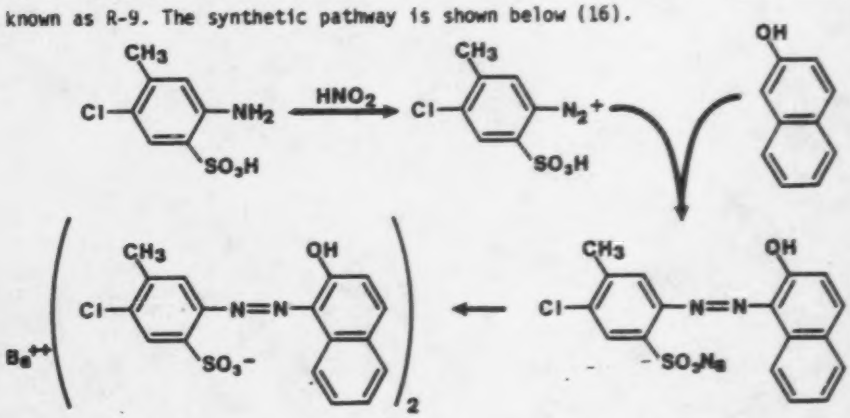
CHAPTER 6. D&C RED NO. 9 (R-9)

I. CHEMISTRY

D&C Red No. 9 (CAS 5160-02-1) (CI 15585:1) (R-9) is a water-insoluble monoazo color additive which is the barium salt (2:1) of 5-chloro-2-[(2-hydroxy-1-naphthalenyl)azo]-4-methyl-benzenesulfonic acid (FDA also terms it the barium salt of of 1-(4-chloro-o-sulfo-5-tolylazo)-2-naphthalenol). It is commonly used as pure color and in a lake form. Its structure is shown below (100).



R-9 is synthesized by diazotization of Red Lake C amine and coupling with 2-napthalenol to produce D & C Red No. 8 (R-8). This color additive is then treated with barium chloride to produce the barium salt of R-8, known as R-9. The synthetic pathway is shown below (16).



FDA certification requires that each color additive lot meet the following specifications (13):

Volatile matter, not more than 5.0 percent.
Ether extracts (isopropyl ether), not more than 0.5 percent.
Red Lake C Amine, not more than 0.2 percent.
Beta-naphthol, not more than 0.2 percent.
Chlorides and sulfates of sodium, not more than 6.0 percent.
Oxides of iron and aluminum, not more than 1.0 percent.
Pure dye (as determined by titration with titanium trichloride), not less than 87.0 percent.

As discussed in Chapter 1, the methods required by FDA for certification are not rigorous, and do not fully characterize the purity of the color. In addition, the methods for the two starting materials are for soluble impurities only and may underestimate the levels of impurities trapped within the crystal structure of this insoluble pigment (16).

A FDA report (16) describes the impurities likely to be present as Red Lake C Amine (2-amino-5-chloro-4-methylbenzenesulfonic acid) and its many possible isomers and impurities unique to each synthetic method, 2-naphthalenol, and the barium salt of 4-(4-chloro-2-sulfo-5-tolylazo)-1--naphthalenol (also termed 4-naphtholazobenzene-4-methyl-5-chloro-1--sulfonate) (a subsidiary color). Other nitroaromatics, subsidiary colors, by products, and degradation products were also listed as possibly present. The Environ report (11) states that, in addition to the two starting materials, other likely impurities are 4 related subsidiary colors. Also, impure isomers of the starting amine may be present in small quantities. Unsulfonated aromatic amines could conceivably be present in isopropanol extractables, but at very low concentrations. Commercial pigment lots were shown to contain the starting materials and the subsidiary color listed above.

Naganuma et al. (22) defined a good methodology to investigate the possible impurities in R-9, including positional isomers of the starting materials and the subsidiary colors produced from these isomers. The data show that the majority of the impurities present in R-9 can be attributed to the impurities present in Red Lake C Amine. Analysis of four lots of R-9 from US manufacturers showed that these amine impurities were present at 30-84 ppm. (NOTE: The pigments analyzed by Naganuma were NOT used in the bioassays). This paper also proposed a cost-effective method of synthesis of Red Lake C Amine and R-9 that has been scaled up for commercial use. The major change involves a purification of the Red Lake C Amine prior to diazotization and coupling with 2-naphthalenol. Other investigators reported 0.1-0.5% 4-(4-chloro-2-sulfo-5-tolylazo)-1-naphthalenol in three commercial samples of dye from the US (23).

The questions of color additive purity and the presence of impurities in the lots of color additive used in the two bioassays discussed below, and in the skin penetration studies also discussed below, were partially answered by CTFA in their submission of a report from A. D. Little on "Spectroscopic and Radiochemical Analyses of D & C Red No. 9". This report is discussed below in detail (24).

Color additive lots of R-9 used in the Battelle (NCI sponsored) rat bioassay (101) (FDA Certified lot no. Z8054, 89.8% color), the Litton Bionetics (CTFA sponsored) rat bioassay (80) (FDA Certified lot no AA3779, 76% color), and the ^{14}C-labelled pigment used in the skin penetration studies (45) (Amersham-U-(^{14}C)-R-9) were investigated, along with the starting materials and 4 subsidiary colors (all Red Lake C Amine isomers).

Two analytical methods were described in the report, Thin Layer Chromatography (TLC) and HPLC. The TLC system used Silica Gel 60 with fluorescent indicator, two solvent systems, and visualization by eye in the visible and ultraviolet range. Radiochemical determinations were made on scrapings from plates. The HPLC method utilized a Radial Pak C-18 column, an isocratic solvent system and dual wavelength detection at 254 and 490 nm. A compound must produce a peak at both wavelengths in order to be measured, according to the report. Fractions were collected and counted for radioactivity. This system was designed only to look at colored impurities.

Results from TLC methods described were not reported; all data were generated by the HPLC method. The color additive used in the Battelle study was found to be 98.8% "pure" (area percent) with several other colored bands seen (it was reported by FDA as 89.8% color). The color additive used in the Litton studies was found to be 97.4% "pure" (area percent) with 7 other colored bands seen (it was reported by FDA as 76% color). Amine and non-azo impurities would not have been detected by this method.

The ^{14}C-labelled pigment was found to be 99.1% dye with 4 other colored bands when analyzed by HPLC. When the same pigment was analyzed for radiochemical purity, 95.6% of the radioactivity was associated with R-9. Eight other radioactive bands including Red Lake C Amine, and two other non-azo compounds were found.

This study was not designed to look at non-colored impurities; however, the color purity is better defined than by just the non-chromatographic FDA certification method. The impurities, however, are much higher than the FDA certified analyses, especially for the lot used in the Litton studies. One also questions why the TLC data were not reported. Other investigators (22) have done definitive work with TLC.

II. METABOLISM

Two radiolabeled preparations have been synthesized; one labeled with ^{14}C in the benzene ring and the other labeled with ^{14}C in the naphthalenol ring. After administration of either preparation added to the diet in a concentration of 3000 ppm (0.3% of the diet) about 54% of the dose of the ^{14}C-naphthalenol label and about 35% of the dose of ^{14}C-benzene label were excreted into urine within 48 hours (102). The compound is insoluble in water and there is no evidence that there would be a dose-dependent rate of dissolution of the compound in the gastrointestinal tract. Very little of the parent compound could be detected in the urine; instead the radiolabel in the urine appears to be associated predominantly with three metabolites. One of the metabolites containing the ^{14}C-naphthalenol label has been tentatively identified as 1-amino-2-naphthalenol and the other as an unidentified conjugate. The principal metabolite containing the ^{14}C-benzene label has been tentatively identified as Red Lake C Amine. Both metabolites would be expected on reduction of the azo-group. But it is not clear whether the reduction occurred predominantly in the gastrointestinal tract and the metabolites were then absorbed or whether the parent compound was absorbed and then eliminated in the liver predominantly by azo-reduction and biliary excretion. Unfortunately, the experiments were not designed to evaluate the two mechanisms or to determine the bioavailability of the compound.

Some of the ^{14}C-naphthalenol label appears to be covalently bound to erythrocytes, possibly through the formation of a chemically reactive metabolite of the 1-amino-2-naphthalenol. Although the investigators suggest that the binding of the metabolite to erythrocytes might lead to the destruction of the erythrocytes in the spleen and thereby cause splenic injury, the hypothesis has not been adequately explored. Nevertheless the fact that neither R-8 or R-9 are mutagenic in bacterial systems (see below), suggest that the reactive metabolite formed from 1-amino-2-naphthalenol does not rapidly combine with DNA. This compound is not mutagenic in bacteria. However a number of the dyes which are reduced to this compound (such as O-17) are mutagenic, implying that the other amines such as 2,4-dinitrobenzeneamine generated may account for the mutagenicity of these other dyes.

III. SHORT-TERM TESTS

Relatively little information has been published about this dye.

A. Mutagenicity

R-9 was negative in TA98, 100, 1535 and 1537, with and without S9 activation (68), and R-9 lake from another source was inactive in the same strains, plus TA1538 (71).

B. DNA Damage/Repair

R-9 supplied by CTFA did not induce DNA synthesis over a wide dose range *in vitro* or after *in vivo* activation at high doses using hepatocytes (103).

C. Other

There were no data from chromosomal damage or transformation assays.

D. Significance

There is no evidence of mutagenicity in bacteria for this dye or induction of DNA synthesis in hepatocytes. Other systems have not been tested. There is no evidence for genetic toxicity of this dye, either by itself or as part of a lake.

IV. COMPARATIVE TOXICOLOGY

A. Negative Studies

1. Rat - R-9 was given at 0.01, 0.05, 0.25 and 1% of the diet to 25 male and 25 female Osborne-Mendel rats for two years. Although no oncogenic effect was noted, splenomegaly and other splenic lesions were noted, especially in rats on the two highest dose levels (104).

   Groups of 60 male and female and then 70 male and female (2nd generation) Charles River SD rats received 0.01, 0.02 or 0.05% of R-9 in the diet in a two-generation study for a period up to 30 months (105).

   In a second study on a similar protocol, (the LBI study), 70 male and female rats were fed 1.0% of the color additive following in utero exposure. Splenic lesions were noted in the male rats fed 1% of R-9 (105).

2. Mouse - In the NCI study, R-9 was given at 0.1 or 0.2% to groups of 50 male and 50 female B6C3F1 mice for 103 weeks. At the high dose there was a minimal change in body weight. No oncogenic effect noted (106).

   Charles River CD-1 mice (60 male and 60 females at each level) received 0.005, 0.025, or 0.1% of R-9 in the diet for 24 months. Neoplastic effects were not noted (105).

   In a second study (the LBI study) 60 male and 60 female CD-1 mice received 0.2% of R-9 for 22 months. Neoplastic effects were not noted (105).

3. Skin Painting - In 50 male and 50 female ICR Swiss-Webster mice 0.1 ml of a 1% solution or suspension of R-9 was applied twice weekly to the skin for 18 months. No oncogenic effect was noted, even in skin (89).

   One-tenth ml of a 1% solution of R-9 was applied weekly to the skin of 50 male and 50 female CF-1 Carworth mice for 26 months. No oncogenic effect was noted, even in skin (98).

B. Positive Study

1. Rat - In the NCI study, R-9 was given at 0.1 or 0.3% in the diet to 50 male and 50 female F344 rats in each group for 103 weeks. Females at the higher dose level showed a 6% weight depression compared to controls. Splenic sarcomas and neoplastic nodules of the liver were increased in male rats (106).

C. Interpretation

1. Interpretation of rat studies

NCI Study

a. Toxicology - R-9 in F344 rats produced no effect on survival when fed at dietary levels of 0.3% but toxic lesions were found in the spleen of male and female rats. These toxic lesions have been described in rats fed diets containing aniline, azobenzene, dapsone and other aromatic amines (107).

b. Pathology - Splenic sarcomas were found in 26/48 male rats fed 0.3% R-9 and in 0/50 control males. These were highly malignant tumors and several metastasized to peritoneal tissues. These are unusual tumors as mentioned. None were seen in female rats fed R-9.

Hepatic neoplastic nodules were found in 7/49 high dose (0.3%) male rats and 6/50 low dose (0.1%) rats and 0/50 control males. High dose (0.3%) female rats had 5/50 nodules while controls had 1/50.

c. Conclusion - R-9 was carcinogenic in male F344 rats and also produced splenic toxic lesions associated with the induced splenic sarcomas. The mechanisms responsible for these tumors are unknown, but they are induced by some aromatic amines and related compounds (86). All may produce methemoglobinemia. This study was adequate for determining the carcinogenicity of R-9 in F344 rats.

The rats were housed together in plastic bottomed cages. R-9 was obtained from H. Kohnstamm & Co. as FDA certified lot Z-8054, 89.8% color. One peak was seen in an HPLC chromatogram. Other assays performed to characterize the dye were elemental analysis, water content (1.58%), IR (consistent with standards), UV (no reference spectra), and TLC. Two TLC systems were used, one detected three impurities, the other 5 impurities. Detection was by visible and UV visualization. The nature of the impurities seen by TLC was not stated. Results from the FDA analysis showed 87% color, 1.8% volatile matter, 0.15% 2-naphthalenol, and less than

0.015% Red Lake C Amine (108).

Studies were performed on stability of the color additive in diets at all dose levels, the homogeneity of the pigment in the feed, and verification of the pigment content of prepared diets. Simple screening methods were used, and were judged adequate for quality assurance purposes. The studies seemed to be well controlled.

One criticism of this study was the group housing of the rats in solid bottom cages where rats could ingest feces likely to contain the metabolites of the dye produced by the azo-reductases of the GI tract. Some of these aromatic amines are established human carcinogens, others are suspect human carcinogens. The amount of coprophagy was likely to be small as animals had access to feed and water at all times. Nevertheless there is the possibility that potentially carcinogenic aromatic amine metabolities could have been ingested. The A. D. Little report, described above, identified some of the colored impurities present in the color additive, but failed to identify non-colored impurities.

LBI study

a. Toxicology - There was some weight depression in male SD rats fed levels of 1% but none in females. There was no effect on survival. There were toxic splenic lesions in males similar to those in the NCI F344 study.

b. Pathology - A few splenic sarcomas similar to those in the NCI study were found in males (4/66) but 2/70 controls also had sarcomas. Adrenal pheochromocytomas occurred in higher incidence (18/70) in 1.0% males than in the control males (11/70), but the difference was not significant.

c. Conclusion- The doses may not have achieved an MTD based on body weights and survival. The adrenal tumor incidence may be due to normal variation.

In this experiment, dye was fed for 30 months in a multi-generation study with in utero exposure. R-9 was supplied by CTFA as FDA certified lot No AA 3779 (Desert Red Batch No. 547530) described as not less than 76% "pure dye". Results from the FDA analyses showed 76% color, 0.3% volatile matter, 0.13% 2-naphthalenol, less than 0.01% Red Lake C Amine and less than 0.5% subsidiary colors (109). There is some question as to how this lot of color additive could be certified since FDA specifications call for not less than 87% "pure dye". No data on the presence of impurities were presented in the bioassay report.

Stability studies of the color additive in diet were performed as well as studies on the homogeneity and quality assurance dose verification. The methods used were adequate to establish quality assurance of dosing.

This study overcomes some of the limitations of the NCI study, but does not provide information on the purity of the dye or the presence of potentially toxic impurities, such as aromatic amines. Studies conducted by A. D. Little, described above, analyzed this lot of color additive for colored impurities, which improves the quality of the study. However, there are virtually no data on the presence of impurities.

2. Interpretation of mouse studies

NCI study

a. Toxicology - R-9 fed at a dietary level of 0.2% failed to cause any signs of toxicity including body weight depression, increased mortality or toxic lesions.

b. Pathology - No lesions were induced.

c. Conclusion - There was no carcinogenic effect at the levels fed.

LBI study

a. Toxicology - There was no body weight depression or effect on survival of mice but mild toxic gastric lesions were induced by R-9 at a dietary level of 0.2%.

b. Pathology - The chemical was found to have a mild irritating effect on the gastric mucosa but no stomach tumors were induced.

c. Conclusion - A neoplastic effect was not noted.

V. SKIN PENETRATION STUDIES

The Franz *in vitro* studies on R-9 (45) used ^{14}C-R-9 obtained from Amersham, UK labelled on the "benzene" ring, presumably on the Red Lake C Amine ring. The stated specific activity was 10.6 mCi/mmol. No data were supplied in the Franz report on the radiochemical purity, however, the A. D. Little report showed a radiochemical purity of 95.6%, with 8 other radioactive fractions seen, including Red Lake C Amine and two other non-azo compounds (24).

Formulations were prepared in oils and talc at 5% dye and dosed as 3 μCi/5 μl/cm^2. A cream blush formulation was prepared at 0.5% and dosed at 1.5 μCi/25 μl/cm^2. Approximately 3 to 4 million DPM of ^{14}C was applied in each preparation. Volpo 20 was used in receptor cells to aid the solubility of the dye.

Most of the material was found in skin washings with good overall recovery of ^{14}C. Counting efficiencies were less than 30% because of the the large amount of aqueous fraction counted in the gelled counting cocktail.

The experimental design seems sound with the exception of the lack of information on radiochemical purity and impurity levels. The characterization of radiochemical impurity by A.D. Little (24) increased the validity of the bioassay, although the identity of the separated impurities would have aided risk assessment deliberations.

VI. SPECIFIC ASSUMPTIONS USED IN RISK ASSESSMENT

1. Assumption: The absorption rate for R-9 is 0.06%/day of the applied amount, except for those products that need adjustment (see Chapter 2, product specific assumptions).

Validity: Would be reasonable if the above rate is a steady state absorption rate. Although the test report (45) indicated that no steady state was reached (page 9), Figures 1 and 2 of the report clearly show a plateau for split-thickness skin chambers with castor oil and cream as vehicles, and a steady-state rate may hence be concluded. The data provided indicate absorption values ranging from 0.016 to 0.064%/day were reached after 2 days.

2. Assumption: The use of Volpo 20 in the receptor of the Franz cell will not significantly alter the skin penetration.

Validity: Probably valid and testable. In vivo there are a number of factors, such as protein binding in blood flowing through the capillary bed, which would remove the dye when it passed through the skin "solubilizing" the color that penetrates.

Option: Conduct parallel studies in vivo and in vitro using saline and 6% Volpo 20.

Impact: Use of Volpo 20 may result in higher observed skin penetrance rates. The effect is not likely to be significant for the risk estimate.

3. Assumption: 50% of the amount of lipstick applied will be swallowed.

Validity: Unknown but testable.

Option: Conduct a study in women on the amount of lipstick swallowed using a radiochemically labeled dye or other tracer. Include measurement of the amount lost due to contact of the lips with other surfaces or to wiping off.

Impact: The Panel agrees with CTFA that 50% is likely to be an overestimation. Since specific data for adjusting the percentage swallowed are not available, however, the Panel accepts CTFA's estimate for the purpose of this review.

VII. RISK CHARACTERIZATION

A. Summary of Dye-Specific Assumptions (Chapter 6.VI)

1. The absorption rate is 0.06%/day of the applied amount, except for those products that need adjustment, which is in agreement with CTFA's assumption.
2. Use the values from the in vitro absorption studies using Volpo 20 without correction.
3. Assume 50% of the lipstick is swallowed, in accord with CTFA.

B. Summary of Product-Specific Assumptions (Chapter 2.III.B)

1. For hair cosmetics, the CTFA-estimate that 2% of the applied amount of dye reaches the skin is an overestimation, requiring a correction factor of 0.6.
2. For nail products, the absorption of dyes is assumed to be zero, as compared to CTFA's assumption that 1% of the dye applied is available for absorption, to which absorption rates are applied.

3. For bathwater products, 1% of the applied dye reaches the skin, where it is available for absorption, as compared to CTFA's assumption of 2%.

4. For "wash-off" products, regardless how short the exposure time, the absorption rate is 25% of that of products used continuously, compared to 50% assumed by CTFA.

5. For products other than "wash-off" products it is assumed that not more than 50% of the amount applied is available for absorption, as compared to CTFA's assumption that 100% of the applied amount is available.

C. CTFA Risk Estimates

From the positive rat study (NCI)

The most sensitive carcinogenic end-point was spleen tumors in males.

a. Calculations using the retrospective usage study by CTFA (9) results give an upper bound on lifetime human risk for external use

= 4.3×10^{-8} for 0.065 μg/kg-day absorbed.

b. Using calculations based on the retrospective usage study, CTFA (9) gives an upper bound on individual risk for lip products subject to ingestion

= 5.1×10^{-6} for 8 μg/kg-day.

D. Revised Risk Estimates

Information on the usage frequency indicates that R-9 is present in 6 groups of products. Application of the dye- and product-specific assumptions to the usage data (Tables 4 and 7, Ref. 9) results in a total absorbed amount of:

1.211 μg/day as an average of the retrospective usage survey;

1.716 μg/day as the upper 90th percentile of the retrospective survey, as compared to the CTFA estimate of 3.44 μg/day.

For ingestion, the use of the dye- and product-specific assumptions and the values of application frequency and amount per application given by CTFA leads to an ingested amount:

86 μg/day as an average based on a survey of ingested lipstick;

415 μg/day as the upper 90th percentile

Both figures are similar to CTFA.

As discussed earlier, it is believed that the prospective survey is less biased than the retrospective study. No results, however, have been provided from the prospective survey so the retrospective study data are used.

At the low dose levels resulting from use of cosmetics, using the linearized multistage extrapolation model, the dose-response curve is linear. This means that the risk of cancer is directly proportional to the dose. The following estimates are based on 53 kg as a lifetime weight average for women, and include the correction factors of 0.8 for skin absorption and 6/7 for incidental ingestion to adjust for the Panel's view on the quantifiable general assumptions (Chapter 2.III.A and 2.V).

	Risk(CTFA/90)*	Risk/90	Risk/Rea
External	4.3×10^{-8}	1.7×10^{-8}	1.2×10^{-8}
Ingested	5.1×10^{-6}	4.3×10^{-7}	8.9×10^{-7}

*- Note, CTFA did not calculate risk estimates based on average exposure levels.

Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.

The risk from ingestion does not include the risk due to absorption of R-9 through the lip surface. Since the skin absorption rate of any of the tested vehicles was less than 0.1%, the incremental risk from absorption through the lip surface would be orders of magnitude lower than the risk from ingestion.

The above risk estimates are based on the reasonable estimates of exposure, whenever the Panel believed that it was possible to make such an estimate. In situations where available data would allow for a choice between "degrees of reasonable estimate", the Panel consistently selected the estimate associated with the higher risk.

If the dose conversion (metameter) from rodents to humans is made on a surface area basis rather than on a body weight basis (mg/m^2-day rather than mg/kg-day) the risk estimates would be raised by a factor of 7 for the estimate based on rat data and 12 for the estimate based on mice. The use of an upper 95% confidence limit for the linearized multistage model utilized in the low dose extrapolation probably leads to an overestimate of risk for rodents. Assuming equal susceptibility for rodents and humans, and also using the most tumor-sensitive site and species, in conjunction with conservative estimates of exposure, are likely to lead to an overestimate of risks for humans.

VIII. CONCLUSION

The NCI study is complicated by the possible ingestion of fecal metabolites. The analyses of dye do not define the levels of non-azo impurities. Both effects are not likely to produce large changes in the risk assessment calculations.

The LBI study had a poorly defined dosing formulation.

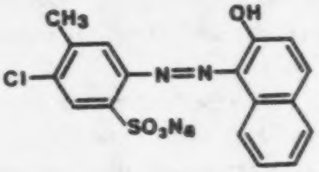
For the skin studies, A.D. Little reported, using HPLC, that 95.6% of the radioactivity was associated with the R-9 peak, with 8 minor peaks including some non-azo material and some starting material. The radiochemical purity seems to be sufficient so that the risk assessment calculations are not significantly altered. The question of higher relative penetration on the facial compared to abdominal skin is addressed in the general section (Chapter 1.V).

As a final word of caution, the risk estimates are based on a recent usage survey and any increase or decrease in the color usage will result in proportionate changes in the estimate of risk. Also it is a CTFA recommendation to limit the dye to two percent in lipstick as it is used in the CTFA risk assessment (FDA regulations allow 3%). It is not binding, and exceeding it could lead to an increase in the risk (however, because of the insolubility of the compound, especially as a lake, an increase in concentration may be meaningless).

CHAPTER 7. D&C RED NO. 8 (R-8)

I. CHEMISTRY

D&C Red No. 8 (CAS 2092-56-0) (CI 15585) (R-8) is a sparingly soluble monoazo color additive which is the monosodium salt of 5-chloro-2-[(2-hydroxy-1-naphthalenyl)azo]-4-methyl-benzenesulfonic acid (FDA also terms it the monosodium salt of 1-(4-chloro-o-sulfo-5-tolylazo)2-naphthalenol). It is commonly used as pure color and as lakes. Its structure is shown below (110). It is sodium salt of R-9 which was previously discussed.



R-8 is synthesized by diazotization of Red Lake C amine and coupling with 2-naphthalenol. The synthetic pathway is identical to that shown above for R-9 except for the last step (16).

FDA certification requires that each color additive lot meet the following specifications (13):

Volatile matter, not more than 10.0 percent.
Ether extracts (isopropyl ether), not more than 0.5 percent.
Red Lake C Amine, not more than 0.2 percent.
Beta-naphthol, not more than 0.2 percent.
Chlorides and sulfates of sodium, not more than 5.0 percent.
Mixed oxides, not more than 1.0 per percent.
Pure dye (as determined by titration with titanium trichloride), not less than 85.0 percent.

As discussed in the general section, the methods of certification are generally not rigorous, and do not fully characterize the purity of the color, as percent of color additive, or the amounts and variety of impurities that may be present including subsidiary colors, side reactions during synthesis and possible degradation products.

A FDA report (16) describes the impurities likely to be present as Red

Lake C Amine (2-amino-5-chloro-4-methylbenzenesulfonic acid) and its many possible isomers and impurities unique to each synthetic method, 2-naphthalenol, and 4-(4-chloro-2-sulfo-5-tolylazo)-1-napthalenol (a subsidiary color). A wide variety of nitroaromatics, possibly subsidiary colors, by products, and degradation products were also listed as possibly present. The Environ report (11) does not address R-8,, but impurities could be expected to be similar to those described for R-9. Commercial pigment lots were shown to contain the starting materials and the subsidiary color listed above.

II. SHORT-TERM TESTS

Relatively little information has been published about this dye. The effects of this dye in short-term tests are expected to be similar to R-9, since the only difference is the cation.

A. Mutagenicity

In addition to the work reported for R-9, R-8 itself was negative in TA98, 100, 1535 and 1537, with and without S9 activation (68). R-8 supplied by FDA was also negative in TA98 as was the dye as part of a lipstick preparation (65).

B. Other

There were no data for DNA damage/repair, chromosomal damage or transformation.

C. Significance

There is no evidence for mutagenicity in bacteria for this dye. Other systems have not been tested. There is no evidence for genetic toxicity of this dye, either by itself or as part of a preparation.

III. COMPARATIVE TOXICOLOGY

No long-term animal assays have been performed with this color additive. However there is little reason to suspect that the material would be different toxicologically from R-9 once it was absorbed. Once the dye reaches the stomach, it is highly unlikely that the dye is maintained as the sodium salt, and R-8 and R-9 are likely to be in the similar, if not identical, salt forms in the gut.

IV. SKIN PENETRATION STUDIES

No skin penetration studies have been performed with this color additive. The increased water solubility may increase skin penetrance so that it may penetrate the skin more rapidly when used as a pure color compared to R-9 used as a pure color. However, when both color additives are used as lakes, there is not likely to be any difference in solubility and thus skin penetration would be expected to be nearly identical.

V. SPECIFIC ASSUMPTIONS USED IN RISK ASSESSMENT

1. Assumption: The experience with R-9 can be used to predict the risk from R-8.

Validity: Reasonable and testable. The risk assessment performed on the closely related color additive, R-9 may have some relevance to R-8. The principal differences between the two color additives: from a chemistry point of view, R-8 is a sodium salt and is more soluble than R-9; from an exposure point of view, there is no exposure information on R-8.

Option: Conduct testing on the toxicity and absorption of R-8.

Impact: The increased solubility may increase penetrance.

VI. RISK CHARACTERIZATION

A. Summary of Dye-Specific Assumption (Chapter 7.V)

1. The dyes are assumed to have similar toxicological effects. Therefore, the risk estimates of R-9 are used to devise a unit risk.

B. CTFA Risk Estimates

CTFA made no estimates of risk from this dye.

C. Unit Risk Estimates

R-9 is a barium salt and R-8 is the sodium salt of the same anion. Given the highly acid milieu of the stomach, there would be no reason for assuming that R-8 would behave differently from R-9 with regard to the cancer response to oral dosing. Once absorbed, therefore, it is reasonable to assume an equal toxicity and an equal dose-response curve.

With regard to absorption through the skin there are differences between the two dyes with regard to their solubility in water. However, it remains unclear whether such differences would have any impact on the absorption rate if R-8 would have been tested at prevailing concentrations in vehicles compatible with marketed products.

It must however be appreciated that there is no exposure information for this color, and the unit risk estimate is based on simple extrapolation from a chemically related dye.

Thus, the nature of this risk estimate is different from those calculated for R-19, O-17, R-9 and R-3. This risk estimate is actually a unit risk, i.e. a risk calculated on the basis of a particular unit of exposure, e.g., a risk of 4.3 X 10^{-8} for an external exposure of 3.44 µg/day to R-9 type dyes. There is no information on actual human exposure, except that it is probably less than R-9 based on production data of the dyes.

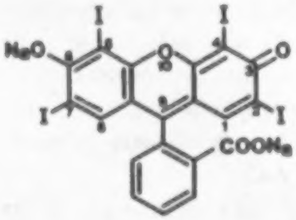
VII. CONCLUSION

The few tests for genetic toxicity that have been performed have been negative. Since it is reasonable to assume that R-8 has the same toxicological effects as R9, any difference in the risk is related to the differences in exposure. The unit risk estimates should be used whenever exposure estimates are available to calculate absolute risk.

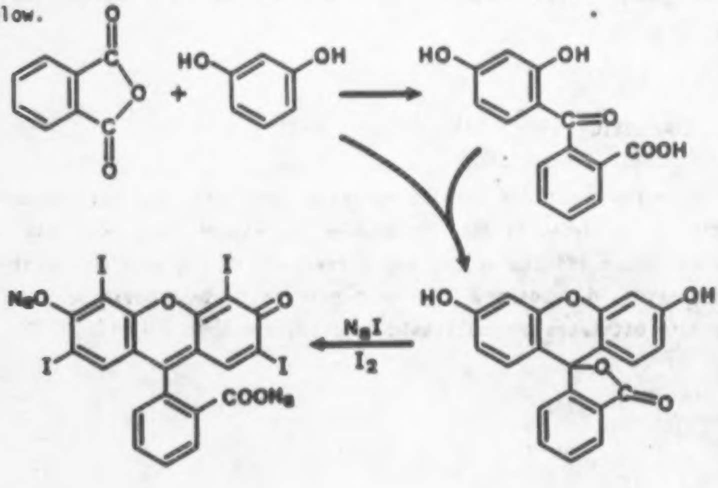
CHAPTER 8. FD&C RED NO. 3 (R-3)

I. CHEMISTRY

FD&C Red No. 3 (CAS 16423-68-0) (CI 45430) (R-3) is a water soluble xanthene dye 3',6'-dihydroxy-2',4',5',7'-tetraiodo-spiro[isobenzofuran-1(3H),9'-[9H]xanthene]-3-one, disodium salt, (known also by the FDA as "principally the monohydrate of 9(o-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthene-3-one, disodium salt, with smaller amounts of lower iodinated fluoresceins"). Its common name is erythrosine and its structure is shown below (17).



R-3 is synthesized by the condensation of phthalic anhydride and resorcinol. The intermediate product 2-(2'4'-dihydroxybenzoyl)benzoic acid is condensed with another mole of resorcinol to produce fluorescein. The fluorescein is then iodinated to produce R-3. The synthetic pathway is shown below.



FDA certification requires that each color additive lot meet the following specifications (13):

Volatile matter, and chlorides and sulfates (calculated as the sodium salts), total not more than 13 percent.
Water-insoluble matter, not more than 0.2 percent.
Unhalogenated intermediates, total not more than 0.1 percent.
Triiodoresorcinol, not more than 0.2 percent.
2-(2',4'-Dihydroxy-3',5'-diiodobenzoyl)benzoic acid, not more than 0.2 percent.
Other lower iodinated fluoresceins, not more than 9 percent.
Lead (as Pb), not more than 10 parts per million.
Arsenic (as As), not more than 3 parts per million.
Total color, not less than 87 percent.

The methods required by FDA for certification are not rigorous, and do not fully characterize the purity of the color, as percent of color additive, or the amounts and variety of impurities that may be present, including subsidiary colors, side reactions during synthesis and possible degradation products (17) as discussed in the general section.

The starting materials and intermediates are possible impurities as well as triiodinated fluorescein. Two reports (11,17) suggest that the following impurities and subsidiary colors may be present: phthalic acid, phthalic anhydride, resorcinol, 2-(2'4'-dihydroxybenzoyl)benzoic acid, iodine, sodium iodide, 2-(2,4-dihydroxy-3',5'-diiodobenzoyl)benzoic acid, triiodoresorcinol, 2,4,7-triiodofluorescein, 2,4,5-triiodofluorescein, 4,5-diiodofluorescein, 2,5-diiodofluorescein, 4-iodofluorescein, 2-iodofluorescein, and fluorescein. Other impurities are possible, depending on the purity of the starting materials. The Environ report (11) suggests similar impurities including starting materials and a variety of incomplete reaction products, primarily mono- di- and tri-iodofluoresceins. HPLC chromatograms obtained from FDA's color laboratories showed the separation of subsidiary colors at 436 and 546 nm. Of the 5-8 peaks seen, R-3 was always the predominant peak with 2,4,5-triiodofluorescein the predominant subsidiary color. Other subsidiary colors identified in "commercial" lots were 2,4,7-triiodofluorescein, 2,7-diiodofluorescein, and a series of small peaks identified as "group". In the chromatograms examined, R-3 was present at 90-94% of the colors detected at the two visible wavelengths (18). Two reports in the literature examined "Erythrosin B" and "Erythrosine" for the presence of subsidiary colors and impurities. Commercial samples of "Erythrosin B" from eight suppliers in the United

Kingdom were examined using TLC and were found to contain numerous colored bands (subsidiary colors) as well as several bands detected with 254 nm UV light. The major subsidiary colors identified were 2,4,5-triiodofluorescein, 2,4,5-triiodo-4',5',6',7'-tetrachlorofluorescein, 4,5-diiodofluorescein, and 4-iodofluorescein. None of the UV absorbing bands were identified (25). Three samples of commercial "Erythrosine" from Japanese suppliers were examined by HPLC using reverse phase chromatography and detection at 230 nm. The results showed the absence of starting materials, except for traces of phthalic acid in one lot, and the presence of 2-3 unidentified subsidiary colors (20). No quantitative data or definitive analyses of impurities were given.

II. METABOLISM

After intravenous administration to rats, R-3 is rapidly eliminated predominantly into bile. The clearance by way of the bile was about 55 times that into urine. Ultimately most of the compound is excreted into the feces. At one time it was thought that high protein bound iodine in blood plasma might reflect the metabolism of the color by a deiodination reaction, but further study revealed that the substance was the dye rather than thyroxine (111). Although there is no definitive evidence that the substance is converted to other metabolites, the possibility that small amounts of the compound undergo metabolism can never be completely excluded. Nevertheless the finding that R-3 is not a mutagen in bacteria may support the view that it is not converted to chemically reactive metabolites that react with DNA, but certainly does not preclude such reactions in other systems. Since the predominant route of elimination is the bile, much of the compound absorbed from the gastrointestinal tract may be returned to the intestine by way of the bile before it enters the systemic circulation. The finding that substantial amounts of the unchanged substance are excreted into feces is not necessarily indicative of dose-dependent absorption. The data are not sufficiently complete, however, to estimate hepatic extraction ratios and thus the relative steady state concentrations in the gastrointestinal tract, the liver, the systemic blood, and extrahepatic organs remain unknown. Nevertheless, we may anticipate that if the compound is as readily excreted in bile of humans, as it is in rats, that the largest area under the curve (AUC) of the aqueous concentration of the compound used as a cosmetic will be in the skin. The aqueous phase of the cells in the thyroid should be among the compartments having the lowest AUC values for the aqueous concentrations of the compounds.

III. SHORT-TERM TESTS

A. Mutagenicity

In Salmonella, TA98 and TA100 (with or without activation with microsomal mix or light), dye obtained from the National Institute of Hygienic Sciences showed no mutational activity (112). Dye obtained from a number of other suppliers over a broad dose range was also without effect both in these assays (65,113-116) and in fluctuation analyses using TA1538 (117,118). Certified food color and dye from Allied Chemical Co. (93% "pure") was also negative for TA98, TA100, TA1535, TA1537, and TA1538 (119,120). There was one report that the dye as formulated by Durand and Huguenin in Switzerland is active in TA 100 (an activity that disappears with S9 activation), but not in TA98, TA1535 and TA1538 (121). In E. coli, although there is some evidence of an effect in reversion of the pro locus (122), in WP2 strain there is no effect either in the trp locus (112,113) or when using a fluctuation analysis (117,118).

In eukaryotes, S. cerevisiae D7 and XV185-14C (a haploid) strains showed a significant effect in one locus with a dose-response (123). However, there was no significant induction of S. chevalieri respiratory-deficient mutants over a wide dose range using erthyrosine from two different suppliers. In fact, there was an inhibition of mutation induced by 4-nitroquinoline-1-oxide (124). Gene conversion did not occur in BZ 34 strain, either in resting or log phase under conditions of the test (a four-hour exposure at 5mg/ml)(125). Gene conversion did occur in the D7 yeast strain over a wide range of doses after a 24-hr exposure (123), although there was no effect on intergenic mitotic recombination in D5 strain in the same experiment. There was no effect in inducing lethal Drosophila mutations or in onion root tip under conditions of light or dark, although there appeared to be an effect in Vicia faba in the light (78).

Thus, there appears to be little evidence for a mutagenic effect of the dye in bacteria or in higher organisms except yeast and Vicia faba. Interpretation of the one report of an effect in TA100 is complicated by the lack of response in other, similar, strains over a wide range of doses in the same experiment and may be a result of impurities in the particular sample or some experimental factor. In yeast, only some strains appear to be sensitive. The reasons for the differential sensitivity may be related to the different endpoints evaluated and the length of exposure to the agent. Also, the authors suggest that the longer growth period used in the D5 mitotic recombination assay may have selected against the expression of a genetic effect resulting from a short exposure time (123); however, there is little support for this contention. The results in Vicia faba may be induced by chemical toxicity since the dye is phototoxic (76).

B. DNA Damage/Repair

Although originally found to be negative in a rec assay (73), which involves damage repairable by a particular enzyme system, the dye was later found to give a positive response if the cultures were exposed to light (112,126,127). Dye from another source, prepared to commercial standards, gave no result (118) with or without light exposure or microsomal activation at a lower dose. In leucocyte cultures exposed to light, there was an inhibition of DNA synthesis (128). In yeast, the results in D7 showing gene conversion, which may be related to a recombination repair, are difficult to evaluate, as indicated above, especially with the negative results in strain D5. Using hepatocytes, over a wide dose range in vitro and at a high dose in vivo, the dye did not induce any DNA repair (103).

There appears to be an effect of light and source on the action of this dye in solution of inducing DNA damage. The effect of source may be related to the presence of impurities in different formulations. This would be consistent with the results seen in light since storage of the solution in liquid phase for some time by the manufacturer could result in generating active species. The results in these asssays should be approached with caution for extrapolation to other biological endpoints. 10^{-4}M is the LC_{50} for human skin cell lines (76) and fetal rat hepatocytes (129), and the toxic effect in culture has been suggested to be related to the consequences of dehalogenation (76).

C. Chromosomal Damage

In vitro there was no increase in chromosomal aberrations in human lymphocytes (128) (although there was a decrease in DNA synthesis) nor mitotic crossing over in D5 yeast (123). There was an increase in chromatid alterations in Ehrlich ascites cells (78) at doses toxic to human cells (although the authors consider the changes mutagenic, there was no evidence the changes were heritable). Positive results in the micronucleus test were reported as evidence of a clastogenic effect in male Swiss mice (130); however no significant effect was seen in a experiment with better controls in Balb/C mice (115).

Again the question of toxicity complicates interpretation, especially for unusual tests. Dying cells release compounds which have complex effects on surrounding cells. It is not clear that the chromosomal effects on cells are a result of direct action on the genome.

D. Transformation

In a transformation assay in Fischer rat embryo cells, no effect was seen (131).

E. Significance

In sum, it appears R-3 is not mutagenic in bacteria, except possibly in a single *E. coli* strain, or higher organisms, except some strains of yeast or in *Vicia faba.* The mutagenesis is only clearly shown for haploid yeast, and is weak compared to ethyl methanesulfonate. From these results, it appears that any effect is more related to DNA transitions rather than frameshift mutations. The dye is positive in the rec assay after light activation and it affects DNA synthesis. There are chromosomal effects in Ehrlich tumor cells and *Vicia faba,* but not in human lymphocytes. The results in the micronucleus tests are equivocal, but, as a whole, appear to show no consistent effect.

The significance of the short-term tests for prediction of long-term toxicity is not straightforward. Except for one test done before modern standardization, the bacterial results for mutation are negative, with toxicity appearing to be a major factor in the positive response in the recombination assays. In yeast, only some strains and endpoints are positive (132). The haploid reversion mutation assay appears to have accuracy of 0.6 in predicting carcinogenicity (40). The yeast mutation assays are not conducted according to an agreed upon protocol and tend to be redundant to the Salmonella test while the conversion assays are not sufficently consistent and reproducible between laboratories (133). The Ehrlich tumor cell assay is hard to interpret because of the instability of the tumor genome. The *Vicia faba* (134) assays require much more development to be predictive of long-term health effects.

Using a recent approach (41), the short-term test results for the dye were evaluated and predict a probability of carcinogenicity for the dye of 0.12 to 1.7%, a probability as low as sucrose (135). The results suggest that the dye is almost assuredly not a carcinogen acting directly on the genome.

The question of how the toxic effects of the compound, especially the phototoxic effect and the release of iodine, are involved in some of the short-term effects seen is a critical, unanswered one. The effect of toxicity in the assays for genetic damage should be clearly separated from a direct effect on the genome, which is difficult to do for many of these observations since the exposures which are effective seem to be toxic ones.

IV. COMPARATIVE TOXICOLOGY

A. Negative Studies

1. *Rat* - R-3 was given at 4% of the diet to a total of 10 male and female Wistar rats for 2 years. One case of hepatic cirrhosis was noted (82).

   R-3 was given at 0.5, 1.0, 2.0 or 5.0% of the diet to groups of 12 male and 12 female Osborne-Mendel rats for 2 years. Growth depression was noted in rats on the 5% level. Spleen weights were decreased. No neoplasms were attributed to the treatment. Subcutaneous injections of R-3 solutions (total dose 12 mg/rat) in 9 male and 9 female rats yielded no tumors at the injection site after 2 years (136).

   R-3 was given at 0.1, 0.5 and 1% of the diet to groups of 70 male and 70 female Charles River rats in a two-generation study which lasted for 24 months. No oncogenic effect was noted (137).

R-3 was given at 0.25, 1, and 4% of the diet to groups of 25 male and 25 female CD rats (at each level) in a three-generation study. There were decreases in body weights of some of the treated groups (4% level). No compound-related effects were noted in the F3b generation (138).

2. Mouse - R-3 was given at 0.3, 1 and 3% of the diet for 24 months to 60 male and 60 female Charles River CD mice in each group. Body weights were decreased slightly at the 3% level. No oncogenic effect noted (139).

3. Gerbil - R-3 was fed to groups of 15 or 16 Mongolian gerbils at 1, 2, or 4% of the diet for 105 weeks. In addition, groups of 20 to 26 male and female gerbils were intubated twice weekly with 200, 750 or 900 mg/kg of R3 by stomach tube for 97 weeks. Enlargement of the thyroids occurred in animals on the 1-4% dietary levels but neoplasms were not noted (140).

4. Dog - R-3 was fed to groups of 3 male and 3 female beagle dogs at 0.5, 1.0 or 2% of the diet for 2 years. No effects due to ingestion of the color additive were seen (136).

5. Skin painting study - In 50 male and 50 female ICR Swiss-Webster mice, 0.1 ml of a 1% solution of R-3 was painted on skin twice weekly for 18 months. No oncogenic effect was noted, even in the skin (89).

B. Positive Study

1. Rat - R-3 was given at 4% of the diet for 24 months to 60 male and 60 female (F_0) and 70 male and 70 female (F_1) CD rats which had been exposed in utero. Body weights of treated rats were lower than those of controls. Thyroid weights were increased in treated F_1 males, and the incidence of thyroid follicular tumors was increased (141).

C. Interpretation

1. Interpretation of rat study

a. Toxicology - At the highest dietary dose level (4%), R-3 caused moderate body weight gain depression as compared with controls. There was no effect on mortality. Toxic lesions were seen in the thyroid glands of male F_1 rats which appeared to represent a goitrogenic effect of R-3 on the thyroid gland. These doses led to increased thyroid weights in males.

b. Pathology - Thyroid tumors (follicular adenoma or carcinoma) were found in 18/70 4% males and in only 1/70 control males. Only 3 of 18 rats with thyroid follicular cell tumors had a carcinoma of these cells.

c. Conclusion - Although R-3 at 4% of the diet with in utero exposure induced some weight depression, only a relatively low incidence of induced thyroid tumors was seen. Thyroid toxic lesions were also relatively mild and mortality was not affected. The study does show that R-3 is a goitrogen and thyroid carcinogen in rats.

R-3 was obtained from CTFA as FDA certified lot no. AA 2459 (733 Erythrosin), with a stated color content of 90% (dark red powder). No data were provided in the bioassay report on the presence of impurities or subsidiary colors that may have been present. FDA certification analyses of this lot show 90% color, 3.6% volatile matter, 7% inorganic salts, 0.19% sodium iodide, 0.07% insoluble matter, and nondetectable levels of phthalic acid, 2-(2',4'-dihydroxy-3',5'- diiodobenzoyl)benzoic acid and ether extractables. Analyses of subsidiary colors showed 4.66% 2,4,5-triiodofluorescein, 0.33% 2,4,7-triiodofluorescein, 0.2% "x", and 94.8% R-3 (19).

Dietary quality assurance studies were performed. The rat diet showed reasonable stability using an extraction-colorimetric method to monitor color concentration. Validation of the dosing formulations at regular intervals, as well as color-diet homogeneity testing were also adequately performed. The study seemed to be well controlled.

The purity of the dye dosed is not stated in definitive terms. All that is shown is that the dye was an FDA certified lot of "90% purity". No impurities were reported, however, the FDA certification analyses showed that the principal impurity was 2,4,5-triiodofluorescein. It is unlikely that significant amounts of identified impurities were present to the extent that the risk assessment would be significantly altered. The conduct of the study from the quality assurance standpoint as it relates to dose was acceptable.

2. Interpretation of mouse study

a. Toxicology - R-3 fed at a dietary level of 3% produced mild body weight gain depression in both sexes of mice. The weight depression in females, however, occurred only after 40 weeks on the study. There seemed to be no significant effect on survival of the mice. No histological lesions were seen.

b. Pathology - No induced lesions were seen.

c. Conclusion- No evidence is presented for the carcinogenicity of R-3 in mice.

V. SKIN PENETRATION STUDIES

The Franz in vitro studies (46) used ^{14}C-R-3 obtained from the Pathfinder Laboratories, with a specific activity of 4.53 mCi/mmol. Although the report from Pathfinder assured the radiochemical purity of the labelled dye (142), the data shown, an HPLC tracing with detection at 254 nm, simply showed that the material synthesized was, indeed, R-3. These data were totally inadequate to determine whether the radioactive label was actually incorporated in the material termed R-3. In light of this, the skin penetration studies are impossible to interpret since it is not certain that the material that penetrates the skin is R-3. Any quantitation is impossible. There is the possibility of uncolored ^{14}C labeled starting materials. There are concerns about the low counting efficiencies reported, and the lack of skin coloration in the presence of significant ^{14}C, as stated in the Franz interview (49).

Therefore, there is no adequate study of skin penetration of the dye.

VI. SPECIFIC ASSUMPTIONS USED IN RISK ASSESSMENT

1. Assumption: For aqueous or ethanol/water solutions, and oil/water emulsions, the absorption rate is 1%, and for talc 0.002% (i.e., the R-19 data) of the applied amount of dye, except for those products

that need adjustment (see product-specific general assumptions).

Validity: Unknown and simple and easy to test. Since there is no adequate study available to evaluate this assumption, use was made of the data available for R-19, another xanthene, water-soluble dye, as a model for R-3. Being a larger molecule, R-3 probably does not penetrate the skin more effectively than R-19.

Option: Either-

a. Conduct in vivo tests for extended periods of time;

b. Repeat the in vitro study with live-skin chambers and for extended periods of time with identified material.

Impact: It is unlikely that R-3 penetrates the skin as well as R-19, therefore the absorption estimation based on R-19 probably overestimates the exposure.

2. Assumption: 50% of the amount of lipstick applied will be swallowed.

Validity: Unknown but testable.

Option: Conduct a study in women on the amount of lipstick swallowed using a radiochemically labeled dye or other tracer. Include measurement of the amount lost due to contact of the lips with other surfaces or to wiping off.

Impact: The Panel agrees with CTFA that 50% is likely to be an overestimation. Since specific data for adjusting the percentabe swallowed are not available, however, the Panel accepts CTFA's estimate for the purpose of this review. However, CTFA's estimate of 14.5 mg lipstick per application x 2.86 applications per day x 1% concentration x 50% swallowed results in 3.9 µg/kg-day and not in 5.5 µg/kg-day.

VII. RISK CHARACTERIZATION

A. Summary of Dye-Specific Assumptions (Chapter 8.VI)

1. For aqueous, ethanol/water, and oil/water based products the absorption rate is 1%/day, for talc 0.002%/day except for the products requiring adjustment (Chapter 2.III.B). This assumption is the same

as CTFA's for liquids, and 0.01 times the value for talc.

2. It is assumed 50% of lipstick is swallowed.

B. Summary of Product-Specific Assumptions (Chapter 2.III.B)

1. For bathwater products, 1% of the applied dye reaches the skin, where it is available for absorption, as compared to CTFA's assumption of 2%.

2. For "wash-off" products, regardless how short the exposure time, the absorption rate is 25% of that of products used continuously, compared to 50% assumed by CTFA.

3. For products other than "wash-off" products, it is assumed that not more than 50% of the amount applied is available for absorption, as compared to CTFA's assumption that 100% of the applied amount is available.

C. CTFA Risk Estimates

1. From data for thyroid follicular tumors in male Charles River CD rats.

The data were combined for the two IRDC studies. Due to an interim sacrifice at one year, and since no thyroid tumors were observed before one year, the number of animals at risk was taken to be the number of survivors at one year.

a. The CTFA estimate of an upper bound on lifetime human risk for external use based on the prospective usage study (10) is

$= 3.2 \times 10^{-8}$ for 0.21 µg/kg-day absorbed.

b. CTFA calculated an upper bound on lifetime human risk for lip products subject to ingestion (10)

$= 8.1 \times 10^{-7}$ for 5.5 µg/kg-day absorbed.

D. Revised Risk Estimates

Information on the usage frequency of products containing R-3 indicates that 5 product categories belong to products with an assumed 1% absorption per day, 3 categories are talc-based products, and 2 are bath products. Application of the above 2 groups of product- and dye-specific assumptions to the Tables 3 and 7 of the CTFA risk assessment report (10) results in a total absorbed amount of dye per person per day of:

0.88 μg/day = 0.0166 μg/kg-day as an average of the prospective survey;

0.9016 μg/day = 0.017 μg/kg-day as the upper 90th percentile of the prospective survey;

1.867 μg/day = 0.0352 μg/kg-day as an average of the retrospective survey;

1.914 μg/day = 0.0361 μg/kg-day as the upper 90th percentile of the retrospective survey.

The comparable CTFA's estimates are 6.650, 11.3, 10.7, and 20.343 respectively. In lip products, the daily absorbed dose is 0.20 mg/day or 3.9 μg/kg-day for the 90th percentile. The average dose, according to a survey of lipstick ingestion, is 0.038 mg/day.

The prospective study will be used to estimate usage for the reasons discussed above. At the low dose levels resulting from use of cosmetics, using the linearized multistage extrapolation model, the dose-response curve is linear. This means that the risk of cancer is directly proportional to the dose. The following estimates are based on 53 kg as a lifetime weight average for women, and include the correction factor of 0.8 to adjust for the Panel's view on the quantifiable general assumptions for skin absorption and 6/7 for incidental ingestion (Chapter 2.III.A and 2.V).

	Risk(CTFA/90)	Risk(CTFA/Avg)	Risk/90	Risk/Rea
External	3.2×10^{-8}	1.9×10^{-8}	2.0×10^{-9}	2.0×10^{-9}
Ingested	8.1×10^{-7}	NR	4.9×10^{-7}	9.1×10^{-8}

NR- Not reported

Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.

Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.

The above risk estimates are based on the reasonable estimates of exposure, whenever the Panel believed that it was possible to make such an estimate. The major differences between the CTFA and Panel estimates are related to the differences in the exposure resulting from talc products, which is much less when a lower absorption is assumed. In situations where available data would allow for a choice between "degrees of reasonable estimate", the Panel consistently selected the estimate associated with the higher risk. For this dye, unlike R-16, O-17 and R-9, there was no adequate study of skin penetrance, so the absorption of a dye in the same chemical class was used. Since this dye is a larger molecule, this model probably overestimates penetrance.

If the dose conversion (metameter) from rodents to humans is made on a surface area basis rather than on a body weight basis (mg/m^2-day rather than mg/kg-day) the risk estimates would be raised by a factor of 7 for the estimate based on rat data and 12 for the estimate based on mice. The use of an upper 95% confidence limit for the linearized multistage model utilized in the low dose extrapolation probably leads to an overestimate of risk for rodents. Assuming equal susceptibility for rodents and humans, and also using the most tumor-sensitive site and species, in conjunction with conservative estimates of exposure, are likely to lead to an overestimate of risks for humans.

VIII. CONCLUSION

The color purity of 90% by FDA certification in the long-term assays does not adequately define the nature of the total dye content. The amounts of organic impurities and subsidiary colors are defined by FDA certification methods. The starting materials and subsidiary colors found in the lot of R-3 evaluated were not present in large quantities except for 2,4,5-triiodofluorescein (4.4%) and are generally not suspected of being strong carcinogens. The degree of data of carcinogenicity of the color additive is relatively weak. One could conclude that the presence of impurities or subsidiary colors may not significantly affect risk assessment calculations.

The lack of any information on the radiochemical purity of the dye makes the skin penetration study impossible to interpret. Therefore, the data concerning R-19 were used. The question of the preferential penetration through facial compared to abdominal skin was addressed in the general section (Chapter 1.V).

The use of R-19 data probably leads to an overestimate of exposure for skin absorption.

Stability studies of the compound "on the shelf" will be helpful for the clearer understanding of the toxic effects of R-3, especially when the phototoxic properties of the dye are considered. This, and an adequate skin absorption study using live animals (e.g., pig) or people (using dye labelled with non-toxic tracers such as the heavy, non-radioactive isotopes of carbon, nitrogen, etc.) would be helpful in estimating the risk.

CHAPTER 9. SUMMARY OF RISK CHARACTERIZATION

I. INTRODUCTION

Chapters 2 through 8 have dealt with issues of exposure to dyes and associated risk. In order to obtain a better perspective on the very complex and multifaceted problem of assessing exposure and toxic effect of the dyes, it was imperative to search for the many obvious or hidden, explicitly stated or implied assumptions associated with risk assessment of the dyes. In dissecting the presented problem into the smallest possible components, for which separate solutions might be formed, the Panel opted for starting with formulating the assumptions according to CTFA's line of reasoning (it should be emphasized, however, that CTFA made these assumptions to, presumably, derive a conservative risk estimate, while not necessarily supporting them). This was followed by a careful analysis of the validity of the statements, the possible alternatives to dealing with the gaps in knowledge and lack of information, and the quantitative assessment of the impact of the assumption on the magnitude of the risk of cancer, assuming that the dyes do pose such a risk to humans.

While evaluating the many kinds of uncertainties in hazard identification, exposure assessment, and dose-response assessment, the Panel developed the view that, rather than limiting its role to analyzing CTFA's lines of reasoning, it attempt to use its analysis to generate modified risk estimates. This includes an estimate of the absorbed dose based on more "reasonable" assumptions that those used in the CTFA assessments. Both a 90th percentile- and an average usage- dose are presented for comparison in the risk characterization section in the various dye chapters.

This chapter presents a summary of the assumptions necessitated by the uncertainties in risk assessment of the 6 dyes of concern, which are critical to the ultimate calculation of the risk of cancer. For this purpose, the various assumptions have been categorized according to the degree of difficulty in quantifying their impact on the risk estimate. It is obvious that with increasing degree of difficulty there will be a widening divergence in opinions about the scientific value of the estimates. The Panel is fully aware of the relative value of expressing exposure and risk in actual numbers, and would like to emphasize that most of these numbers are not presented with implied accuracy and precision. Also, they cannot be separated from the discussion surrounding them in the various chapters. Even the application of statistical confidence limits cannot remedy the fact that the numbers are based on assumptions-guided interpretations of observational data or even on "a reasonable guess by scientists". This chapter is simply a convenience and should not be misused by considering the values summarized here out of the context of the chapter surrounding them.

The estimation of the frequency of the use of dye-containing cosmetics is an excellent example of a situation, in which a set of observed data may falsely be interpreted as reflecting the truth. Two surveys were conducted, and the resulting estimates of the total amount of dye absorbed per person are relatively close to each other. Yet calculating a statistical confidence in the outcomes, for the purposes of comparison, is meaningless, since the two populations studied were essentially different because of confounding factors. Scrutinized further, the study populations not only differed from each other, but also from the general population of users of cosmetics, which the surveys were used to model. Yet, the Panel chose to utilize the data to approximate the real exposure, feeling that they help establish some gross limits on usage. For dealing with such problems, the Panel felt that with a judicious approach, cautious utilization, scientific objectivity, and open mind, decisions can and must be taken. The following is a summary of the results of this effort.

For judging the implied values of the above risk estimates, it should be re-emphasized that they are based on the following basic principles:

1. Given an exposure and given the dyes are carcinogenic, the magnitude of the risk of cancer can be calculated using some dose-response curve. The correct mathematical model for this is unknown, and the model used by CTFA and accepted by the Panel is no guarantee that the estimate is correct, and is not necessarily more correct than an estimate resulting from some other extrapolation model.
2. The risk estimate is an "upper bound" of the risk in the rodent strain under conditions of the test, meaning that in all likelihood the true risk is lower. How much lower is unknown, and the upper bound should not be conceived as the upper limit of the classical statistical confidence limits of a point estimate. The "upper bound" may be

several orders of magnitude higher than the true risk, depending on the applicability of low-dose linearity to the biological phenomenon of cancer induction by the dyes.

3. It is, moreover, assumed that exposure through the skin has an effect equal to that of oral exposure, given the same absorbed amount of dye. There are very little data to support this assumption, and the impact that inaccuracies in the assumption might have on the risk estimate is, therefore, unknown.
4. When possible, estimates of upper bound risk have been based on reasonable estimations of exposure. In situations characterized by the presence of options between reasonable estimates, the Panel has consistently chosen the ones than are likely not to underestimate the risk. Overall, as a result, the Panel's risk estimate can be characterized as a reasonably conservative estimated upper bound of the true risk.
5. The risk estimate does not deal with the cardinal question whether or not the dyes reviewed are human carcinogens, and does not account for biological variability within and between species. Assuming that the animal model is appropriate for the human population, and because conservative assumptions were used regarding absorption, exposure, and low-dose extrapolation, it is more likely that human risk has been overestimated rather than underestimated.

II. RELATIVELY EASY QUANTIFIABLE ASSUMPTIONS

A. Assumptions Applicable to All Dyes and Products

1. The duration of exposure is not more than 6/7 of the human lifespan (Chapter 2.II.A6). Correction factor for the CTFA estimate is 6/7.
2. Consumers used colored products with an average dye concentration equal to 0.25 times the maximum concentration in commercial products (Chapter 2.III.A5). Correction factor for the CTFA estimate is 0.25.
3. Absorption tests using abdominal skin underestimate the overall absorption rate by a factor of not more than 3. (Chapter 2.II.A6). Correction factor for the CTFA estimate is 3.
4. The absorption rate equals the steady-state rate observed in the in

vitro test. In the absence of a steady state, the maximum rate at the end of the 3rd test day is accepted (Chapter 2.II.A7). No correction is needed.

5. The CTFA usage surveys are representative of the general population. Since it is understood that an individual risk to users is what is required, no correction is needed although it would be an overestimate for the general population.

6. Over a lifetime, the average woman is assumed to weigh 53 kg (Chapter 2.IV.3). No correction is needed.

B. Product-Specific Assumptions

1. Only 1.2% of the dyes in hair cosmetics reaches the skin (Chapter 2.II.B1). Correction factor for the CTFA assessment is 0.6.

2. Dye from nail products will not be absorbed (Chapter 2.II.B2). Correction factor for the CTFA estimate is 0 (zero).

3. Of bathwater products, 2% will reach the skin (Chapter 2.II.B3). No correction factor is needed.

4. Of products used for brief periods only (wash-off products), 25% will reach the skin (Chapter 2.II.B4). Correction factor for the CTFA estimate is 0.50 (also bathwater products are included).

5. For non-wash-off products, 50% will reach the skin (Chapter 2.II.B5).

C. Dye-Specific Assumptions

1. The absorption rate of R-19 from emulsions is 0.25%/day (Chapter 3.V.1). Correction factor for the CTFA estimate is 0.5.

2. The absorption rate of R-19 from mineral oil based products is 0.25%/day (Chapter 3.V.2). Correction factor for the CTFA estimate is 0.5.

3. The absorption rate of R-19 from castor-oil-based products (Chapter 3.V.2) is 0.04%/day. Correction factor for the CTFA estimate would be 0.08, but no such products have been identified by CTFA.

4. The absorption rate of R-19 from aqueous products is 1%/day (Chapter 3.V.3). No correction factor is needed.

5. The absorption rate of R-19 from talc products if 0.002%/day (Chapter 3.V.4). No correction factor is needed.

6. The absorption rate of O-17 from creams and oils is 0.005%/day (Chapter 5.V.1). Correction factors for the CTFA estimate is 0.5.

7. The absorption rate of O-17 from talc products is 0.0005%/day (Chapter 5.V.2). Correction factor for the CTFA estimate is 0.5.

8. The use of Volpo 20 instead of saline will not affect rates. No correction factor needed (Chapter 5.V.3, 6.V.2).

9. The absorption rate of R-9 is 0.06%/day, unless product-specific adjustment is required. No correction is needed.

10. 50% of applied lipstick will be swallowed. No correction factor is needed (Chapter 6.V.2; 8.VI.2).

11. Based on R-19, the absorption rate of R-3 from liquid products is 1%/day, and from talc products 0.002%/day (Chapter 8.VI.1). No correction needed for the liquid products, a factor of 0.01 is needed to correct the talc-related exposures..

12. The exposure to R-9 from lipstick is 3.9 µg/kg-day (Chapter 8.VI.2). Correction factor for the CTFA estimate is 0.7.

III. ASSUMPTIONS MODERATELY DIFFICULT TO QUANTIFY

1. The dyes administered in the cancer bioassays were absorbed in the gut at approximately 50% (Chapter 2.IV.1). Correction factor for the CTFA estimate is 2.

2. The carcinogenic effect of the dyes in test animals may have been influenced by impurities, either subsidiary colors that form not more than 5% of the administered dose and have approximately equal absorption or residual starting materials, less than 0.5% of the dye, which can have a potency to induce cancer not more than 5 times the potency and not more than 10 times the skin penetration estimated for the pure dye (Chapter 2.II.14). Correction factor for the CTFA estimate is 1.2.

IV. QUALITATIVE AND DIFFICULT-TO-QUANTIFY ASSUMPTIONS

A. Assumptions Used in Exposure Assessment

General

1. Gut absorption in man and test animal is similar, regardless of chemical concentrations and vehicle used (Chapter 2.II.A1).
2. When comparing routes, the amount that penetrates the skin has the same capacity to evoke a carcinogenic response as material that penetrates the gut (Chapter 2.II.A2).
3. The absorption rate of dyes through the skin can be estimated by using the Franz _in vitro_ skin model (Chapter 2.II.A6).
4. Products containing the dyes of concern form 50% of the total use of such products (Chapter 2.II.A4). Correction factor for the CTFA estimate is 0.5.
5. The _in vivo_ skin-absorbed total amount of dye equals the amount of dye per application times the frequency of application per day times the percent of applied dye absorbed per day (Chapter 2.II.A9).
6. The CTFA usage surveys are representative of the population of users of products containing the dyes of concern. Since males were underrepresented in the survey, and women were more likely to use the products at a higher frequencies and in higher concentrations than men, this assumption overestimates, to an unknown extent, the true exposure of the product-using population. For a given dye, the total exposure is the sum of exposures to products containing the same dye (Chapter 2.II.A10). No correction is needed.
7. The amount of dye-containing product is 5-10 mg/cm^2 per application (Chapter 2.II.A11).
8. The variation in the vehicle used in commercial products is adequately represented in the _in vitro_ tests (Chapter 2.II.A12).
9. In an appropriate vehicle, there is no difference in absorption rate between the pure dye and its lake form (Chapter 2.II.A13).

Dye-Specific

1. The risk posed by R-37 is 0.5 times the risk posed by R-19 on an equal weight basis (Chapter 4.V.1). A correction of 0.5 is used to reflect this difference in weight. However, this also assumes equal exposure, absorption and toxicological effect for R-37 and R-19.
2. The absorption rates, toxicology, and exposure of R-8 are fully comparable to those of R-9 (Chapter 7.V.1).

3. The absorption of R-3 is similar to R-19 (Chapter 8.VI.1).

B. Assumptions Used in Dose-Response Assessment

1. The risk estimated in test animals can be extrapolated to humans on a µg/kg-day basis (Chapter 2.IV.2).
2. The linearized multistage risk model is appropriate for estimating "upper bound" on risk at low doses. (Chapter 2.IV.4).
3. Data from the most sensitive animal species and gender are an appropriate basis for estimating human risk (Chapter 2.IV.5).

V. UNIT AND REVISED RISK ESTIMATES

Based on the above assumptions, a revised risk estimate has been derived and summarized here (actual risk estimates are at the end of each dye chapter). The table legends are:

Absorbed Dose is the estimated dose absorbed from external uses in µg/day.
Ingested Dose is the estimated dose from incidental ingestion of lip products in µg/day.
Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.
Risk(CTFA/Avg) is the CTFA risk estimate at "average" estimates of exposure.
Risk/90 is the risk estimate based on the Panel's calculation at the 90th percentile of exposure.
Risk(Rea) is the risk estimate based on the Panel's calculation of a more reasonable estimate of exposure.
NR means Not reported.
Rat indicates that the data were derived from a rat study.
Mouse indicates that the data were derived from a mouse study.
External indicates estimated risk from the external uses of the dyes.
Ingested indicates estimated risk from incidental ingestion of the dyes.

A. R-19

	Risk(CTFA/90)	Risk(CTFA/Avg)	Risk/90	Risk/Rea
Absorbed Dose	3.27	0.85	1.62	0.42
Rat	2.7×10^{-7}	7.1×10^{-8}	1.1×10^{-7}	2.8×10^{-8}
Mouse	1.3×10^{-7}	3.4×10^{-8}	0.5×10^{-7}	1.3×10^{-8}

B. R-37

There are no data on the usage pattern, skin absorption or toxicology. R-37 is considered to present 0.5 times the risk of R-19 based on a per weight basis, i.e. $0.5 \times 0.8 \times 2.7 \times 10^{-7}$ or 1.1×10^{-7} for 3.27 µg absorbed R-37/day (modeled on the most sensitive strain/species, i.e., the rat).

C. 0-17

	Risk(CTFA/90)	Risk/90	Risk/Rea
Absorbed Dose	0.0208	0.00635	0.00189
Rat	2.1×10^{-10}	5.1×10^{-11}	1.5×10^{-11}
Mouse	0.7×10^{-10}	1.7×10^{-11}	0.5×10^{-11}

D. R-9

	Risk(CTFA/90)	Risk/90	Risk/Rea
Absorbed Dose	3.44	1.72	1.216
External	4.3×10^{-8}	1.7×10^{-8}	1.2×10^{-8}
Ingested Dose	415	415	86
Ingested	5.1×10^{-6}	4.3×10^{-6}	8.9×10^{-7}

E. R-8

There are no data on the usage pattern, skin absorption or toxicology. R-8 is considered to present the same risk as R-9 based on a per weight basis, i.e., $0.8 \times 4.3 \times 10^{-7}$ or 3.4×10^{-7} for 3.44 µg absorbed R-8/day and $6/7 \times 5.1 \times 10^{-6}$ or 4.3×10^{-6} for 415 µg ingested R-8/day (modeled on the most sensitive strain/species, i.e., the male rat).

F. R-3

	Risk(CTFA/90)	Risk(CTFA/Avg)	Risk/90	Risk/Rea
Absorbed Dose	11.3	6.65	0.88	0.90
External	3.2×10^{-8}	1.9×10^{-8}	2.0×10^{-9}	2.0×10^{-9}
Ingested Dose	200	38	200	38
Ingested	8.1×10^{-7}	NR	4.9×10^{-7}	9.1×10^{-8}

G. Conclusion

The above risk estimates are based on the reasonable estimates of exposure, whenever the Panel believed that it was possible to make such an estimate. In situations where available data would allow for a choice between "degrees of reasonable estimate", the Panel consistently selected the estimate associated with the higher risk.

If the dose conversion (metameter) from rodents to humans is made on a surface area basis rather than on a body weight basis (mg/m^2-day rather than mg/kg-day) the risk estimates would be raised by a factor of 7 for the estimate based on rat data and 12 for the estimate based on mice. The use of the upper 95% confidence limit of the linearized multistage model utilized for the low dose extrapolation probably leads to an overestimate of risk for rodents. Assuming equal susceptibility for rodents and humans, and also using the most tumor-sensitive site and species in conjunction with the conservative estimates of exposure, is likely to lead to an overestimate of risks for humans.

Since the risk estimates are based on the assumptions used, these have been identified, and quantitated when possible, so that effects of agreement or disagreement with any of the assumptions can be quantitated.

VI. PERSPECTIVE

It is the Panel's opinion that this report includes the "best judgement" on the risk possibly posed by the external use of the 6 dyes reviewed, while a considerable margin of safety based on absorption and exposure still remains. The following example for R-19 is used to put the above risk estimates and the underlying assumptions in perspective (a similar approach was not possible for the other dyes because of uncertainty in the amount of dye in the appropriate lake).

In the period 1983 - 1984 FDA certified a total of 10801 pounds of R-19. This agrees with an unpublished crude CTFA estimate, communicated to the Panel. CTFA estimated that an average of 270 pounds of color per year and 4497 pounds of lake per year were used for the manufacturing of products for external use in this period (the lakes contained the color in various concentrations, but not to exceed 25%). Dividing the total amount of R-19 over 10 million women, for example, and assuming the absurd situation that all dye is ingested and absorbed rather than applied to the skin, the individual dose would be 3.3 µg/kg-day. The number of consumers is unknown. If there were 20 million users of R-19, this dose would be divided by 2, etc.

In this situation, the dye-specific and product-specific assumptions are eliminated. The estimated absorbed dose of 0.008 µg/kg-day from external uses calculated by the Panel appears to be reasonable when compared to the maximum dose from the total amount of R-19 produced.

With this admittedly absurd possibility as a comparison, it appears to the Panel that the absorption assumptions and the dye- and the product-specific assumptions are not likely to lead to a significant underestimate of exposure and, hence, of risk.

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Appendix A - The charter, agenda and minutes of the panel's meetings

Color Additive Scientific Review Panel
CHARTER

Purpose

The panel is to evaluate the available data, information and views on FD&C Red No. 3, D&C Red Nos. 8 and 9, D&C Red Nos. 19 and 37, and D&C Orange No. 17 and to provide justified answers to the following questions in the form of a final report to the Commissioner of Food and Drugs:

(1) Can valid, quantitative risk assessments be performed for these color additives?

(2) Does the available information support the data analyses and risk assessments that have been performed and are before the agency?

Background

FD&C Red No. 3, D&C Red Nos. 8 and 9, D&C Red Nos. 19 and 37, and D&C Orange No. 17 are dyes that have had a variety of applications in coloring foods, drugs and/or cosmetics. As color additives, these products are subject to the certification provisions of the Federal Food, Drug and Cosmetic Act. During 1984, the following amounts of color additive were certified by FDA: FD&C Red No. 3 (Erythrosine), 241,265 pounds for use in food and drugs (permanently listed) and in cosmetics (provisionally listed); D&C Red No. 8 (monosodium salt of 1-(4-chloro-o-sulfo-5-tolylazo)-2-napthol), zero pounds for use in drugs and cosmetics (provisionally listed); D&C Red No. 9 (Barium salt of 1-(4-chloro-o-sulfo-5-tolylazo)-2-naphthol), 24,571 pounds for use in drugs and cosmetics (provisionally listed); D&C Red No. 19 (3-ethochloride of 9-o-carboxyphenyl-6-diethylamino-3-ethylimino-3-isoxanthene), 6,965 pounds for use in drugs and cosmetics (provisionally listed); D&C Red No. 37 (3-ethostearate of 9-o-carboxyphenyl-6-diethylamino-3-ethylimino-3-isoxanthene), zero pounds for use in drugs and cosmetics (provisionally listed); and D&C Orange No. 17 (1-2,4-dinitrophenylazo)-2-naphthol), 1,083 pounds for use in drugs and cosmetics (provisionally listed).

Because of questions of carcinogenicity that have been raised on the subject of selected color additives, FDA has, on several occasions, recommended removing them from the marketplace. (References 1-5).

Views and information supporting continued marketing of the additives in light of analyses that purport to show minimal risk from their use have been submitted by the Cosmetic Toiletry and Fragrance Association. These include a series of analyses dated October 15, 1982 (D&C Red No. 19, Reference 6), April 15, 1983 (D&C Orange No. 17, Reference 7), August 15, 1983 (D&C Red No. 19, Reference 8), and March 30, 1984 (FD&C Red No. 3, Reference 9). In addition, Environ has submitted (on October 22, 1984, Reference 10) a comprehensive analysis of all issues on the behalf of the Cosmetic Toiletry and Fragrance Association.

Finally, views and information have been submitted to FDA by Public Citizen in the form of a citizen's petition dated December 17, 1984 (Reference 11) recommending FDA action to end the provisional list.

Panel Members

Dr. Ronald W. Hart (Chair)
Director, National Center for Toxicological Research
Food and Drug Administration

Dr. Stan Freni
Center for Environmental Health
Centers for Disease Control

Dr. David W. Gaylor
Director, Division of Biometry
National Center for Toxicological Research
Food and Drug Administration

Dr. James R. Gillette
Chief, Laboratory of Chemical Pharmacology
National Heart, Lung and Blood Institute

Dr. Larry Lowry
Technical Support Branch
National Institute for Occupational Safety and Health

Dr. Jerrold M. Ward
Chief, Tumor Pathology and Pathogenesis Section
National Cancer Institute

Dr. Elizabeth Weisburger
Assistant Division Director for Chemical Carcinogenesis
National Cancer Institute

Panel Operations

The panel will be provided with copies of the references described above in the Background as well as any available information that they request bearing on the issues. The panel will have access to any officials and scientists in FDA that may be required to assist their deliberations. Access, as possible, to other government scientists may also be provided.

The panel will deliberate in convened meetings as called by the Chairman and will prepare a consensus report that specifically addresses the issues presented in this charter.

Time Target

The panel is to forward the final report to the Commissioner no later than eight weeks after the initial meeting (scheduled for May 3). The Commissioner may request the panel to orally summarize the report in a convened meeting. Dr. Paul D. Lepore of the Division of Compliance Policy will act as Executive Secretary for Washington Operations and Dr. Angelo Turturro of NCTR will act as Executive Secretary for Arkansas Operations.
Color Additive Scientific Review Panel

Administrative Record

The administrative record of the panel will include all documents provided to the panel, meeting agenda and minutes, C.V.'s of the panel members, and the final report.

May 1, 1985

Executive Secretary for Washington Operations

AGENDA - Initial Panel Meeting

Members, Color Additive Scientific Review Panel

The first meeting of the Color Additive Scientific Review Panel will be held at 11:30 a.m. on May 3, 1985 in the Commissioner's Conference Room (Parklawn Building, Room 14-65). Dr. Hart has prepared the following agenda:

1.	11:30 - 12:00	Dr. Young
2.	12:00 - 12:30	Dr. Hart
3.	12:30 - 1:00	Distribution of References
4.	1:00 - 1:30	Group Discussion
5.	1:30 -	Plans

Please plan to arrive 15 minutes prior to the meeting so that any last minute paperwork and details can be handled.

Paul D. Lepore

Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowery
Dr. Ward
Dr. Weisburger

May 14, 1985

Executive Secretary

Minutes of the May 3rd Meeting of the
Color Additive Scientific Review Panel

The Administrative Record

The subject meeting was held to receive the official charge, to obtain copies of the resource materials, to develop operating procedures, and to plan future work. All panel members were in attendance.

Chairman Hart opened the meeting with introductions and a directive to the panelists to base their determination on solid science. The Commissioner joined the meeting at 12:05 p.m., welcomed the panelists, stressed the importance of the color additive issues and thanked the panelists for their willingness to help the agency. He summarized the questions that the panel had to resolve as follows:

(1) Based on the available information, can a valid quantitative risk assessment be done, and

(2) If so, what is the estimate of risk?

He said that once the agency had answers to these questions, that any identified risks would be dealt with in accord with FDA's risk management procedures.

In response to questions from the panel, the Commissioner responded that he opted for a panel of government scientists because he was convinced that there are good scientists in government and that a government panel would provide a more expeditious resolution of the issues. He agreed that the issues were difficult but that he was sure that the panel could arrive at an unquestionable conclusion that was scientifically justifiable and fully objective. In this regard, he agreed that the two month time-frame was an ambitious target and that he would be pleased if, at that time, he received a summary of the concensus conclusion reached by the panel. He did state that he wanted a final panel report that reflected concensus and that, when the report was orally summarized to him, he would poll the individual panelists to define the limits, if any, of consensus. He concluded his comments with a clarification that the panel should direct their efforts to estimating the probability of risk to humans and with a commitment to provide whatever help would be needed for the panel to complete its work. The Commissioner left the meeting at this time (12:40 p.m.).

The remainder of the meeting was devoted to general discussion and to planning future work efforts. The following action items were assigned:

o NCTR would assign a librarian to conduct literature searches and to provide hard copy citations and abstracts.

- o The Executive Secretary would obtain, from the Center of Food Safety and Applied Nutrition, an index of the studies that had been submitted in color additive petitions.
- o The Executive Secretary would check what information is available in the SIREN system.
- o The Executive Secretary would obtain a ruling from General Counsel concerning the appearance of outside experts before the panel.

Future meetings of the panel were tentatively scheduled as follows:

May 14, 1985	June 7, 1985 (p.m.)
May 23, 1985	June 13, 1985 (p.m.)
May 31, 1985	June 21, 1985

Paul Lepore

cc: Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

May 6, 1985

Executive Secretary, Color Additive Scientific Review Panel (HFC-230)

Information Request

Director, Center for Food Safety and Applied Nutrition (HFF-1)

The Color Additive Scientific Review Panel held its first meeting on May 3, 1985. From the meeting, Chairman Hart has asked that I request from you a listing of all of the safety studies that have been submitted to the peitions on FD&C Red No. 3, D&C Red Nos. 8 and 9, D&C Red Nos. 19 and 37, and D&C Orange No. 17. I anticipate that the panel intends to also request hard copies of these studies so that they can be thoroughly reviewed.

I have discussed this request with Dr. Flamm and Dr. Dennis and they are moving to assemble the required information.

I thank you for your help in this matter.

Paul Lepore

cc: Dr. Hart
Dr. Turturro
Color Additive Scientific Review Panel Members

May 6, 1985

Executive Secretary, Color Additive Scientific Review Panel (HFC-230)

Request for Legal Opinion

General Counsel (GCF-1)

The Color Additive Scientific Review Panel held its first meeting on May 3, 1985. From the discussion, Chairman Hart has asked that I request a ruling from you on the matter of outside contributions to the panel's work.

Specifically, I understand that outside participation would occur under the following circumstances:

1. Both federal and private experts would be invited to panel meetings to discuss data, information, and views that bear on the panel issues.
2. The experts would make their presentations singly before the panel and they would be in the panel meetings only for the duration of their presentations.
3. The expert appearances and presentations would be made part of the administrative record.

Please advise if this would be a satisfactory procedure. If not, please recommend one.

Paul Lepore

cc: Dr. Hart
Dr. Turturro
Color Additive Scientific Review Panel Members

May 8, 1985

Executive Secretary for Washington Operations

AGENDA - Second Panel Meeting

Members, Color Additive Scientific Review Panel

The second panel meeting will be held at 9:30 a.m., on May 14, 1985, in Room 14-63 of the Parklawn Building. Dr. Hart has prepared the following agenda:

1. Review, correction, and approval of the minutes of the first meeting.
2. Reports on the Action Items from the first meeting
    - o Librarian
    - o Index of color additive petitions
    - o SIREN
    - o Outside participation
3. General discussion
4. Plans
5. Assignments

Paul D. Lepore

Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

May 24, 1985

Executive Secretary

Minutes of the May 14th Meeting of the Color Additive
Scientific Review Panel

The Administrative Record

The purpose of the meeting was to accomplish the items listed in the agenda dated May 8th and to continue the work of the panel. All panel members were in attendance.

The panel reviewed, revised and approved the minutes of the May 3rd panel meeting.

Progress on the Action items that were defined in the first panel meeting was made as follows:

NCTR has identified a librarian for the references in the open literature and computerized searches were made of the various toxicology literature using the following search terms: color additive (specific), metabolism, absorption, transport, carcinogenicity, contaminants, pharmacokinetics, neurotoxicity, mutagenicity and teratogenicity. Computer printouts of the identified references (search date of May 9) were given to the panel members. The panel requested that the data base search be expanded to encompass references under the terms toxicology, pathology, and epidemiology.

CFSAN developed indices of the information contained in the color additive petitions on the various colors. These, too, were provided to the panel members. The indices were accompanied by excerpts, containing a scientific discussion of the issues, from internal draft documents concerning denial of the petitions.

The SIREN petition indexing and information system was described. It was concluded that the information in SIREN would not be as comprehensive nor as complete as the indices already provided by CFSAN. The panel elected not to request a SIREN printout.

The Executive Secretary reported that General Counsel had ruled on the appearance of outside experts before the panel (see Scarlett memo dated May 14, 1985) and that such was possible under certain conditions.

At this point, Dr. Freni indicated that he had been in contact with CTFA concerning an inconsistency in one of the documents on Red 19. The resulting communications are attached.

The panel then directed efforts to reading the computer printouts and the color additive petition indices for the purpose of identifying references pertinent to the panel review. This was done and Executive Secretary Turturro was charged with obtaining hardcopies of references from the computer printout and Executive Secretary Lepore was to do likewise with the references in the color additive petitions. Copies of all references provided to the panel are to be made part of the Administrative Record. It was understood that the copies would be scanned for pertinence to the issues and that the panelists would critically review only the pertinent references.

The remainder of the meeting was devoted to a general discussion of the issues by the panel and of the action steps required to produce a final report. The next meeting was set for May 23 at 9:30 a.m.

Paul Lepore

cc: Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

May 16, 1985

Executive Secretary for Washington Operations

AGENDA - Third Panel Meeting

Members, Color Additive Scientific Review Panel

The third panel meeting will be held at 9:30 a.m. on May 23, 1985, in Room 13-57 of the Parklawn Building. Dr. Hart has prepared the following agenda:

1. Review, correction and approval of the minutes of the second meeting
2. Panelist Reports
3. General discussion
4. Plans
5. Assignments

Paul Lepore

Panel Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

June 3, 1985

Executive Secretary

Minutes of the May 23rd Meeting of the
Color Additive Scientific Review Panel

Administrative Record

The subject meeting was held to hear the panelist reports in their specialty areas, to discuss the assumptions made in conjunction with the various risk assessments and to otherwise continue the work of the panel. Panelist Ward was not in attendance due to a conflicting commitment.

The bulk of the day's discussion was devoted to the risk assessments performed by Drs. Freni and Gaylor. The panelists assessed each of the associated assumptions and attempted to reach a justifiable position.

The following action items were assigned by Chairman Hart:

- The panelists are to continue to review and assess the data and information within their respective areas and to prepare individual draft reports on the science of the issues. The reports are to cite, as necessary, the pertinent literature references.
- The Executive Secretary is to prepare a request to the Director, CFSAN for:
  1. A listing of cosmetic products containing the colors under review as well as the level of the color occurring in the product.
  2. The regulatory definition of carcinogen used by CFSAN.
  3. The appearance at the panel's next meeting of a color chemist from CFSAN.
- The Executive Secretary is to assure that Dr. Ward is briefed on today's meeting and the action items deriving therefrom.
- The Executive Secretary is to arrange for the appearance of the panel's next meeting of Dr. Thomas J. Franz (formerly at the University of Washington, School of Medicine, now with Hoffmann-LaRoche, Inc.) to discuss the percutaneous absorption issues.
- Panelists are to prepare questions on the skin absorption studies performed by Dr. Franz.
- Dr. Hart is to contact Dr. Herb Rosenkranz (Case Western Reserve University) on the mutagenicity issues and to determine whether it will be necessary to invite Dr. Rosenkranz to appear before the panel.

The next meeting of the panel was set for May 31 at 8:00 a.m.

Paul Lepore

May 24, 1985

Executive Secretary, Color Additive Scientific Review Panel (HFC-230)

Requests Arising From the Third Panel Meeting

Director, Center for Food Safety and Applied Nutrition (HFF-1)

Chairman Hart has asked me to request the following items that surfaced at the subject meeting:

1. For the colors under consideration, a listing of their maximum permitted uses in the various cosmetic products.
2. The definition used by CFSAN to classify a chemical as a carcinogen for regulatory purposes, and
3. The presence at the next panel meeting (May 31, 9:00 a.m., Room 14-63, Parklawn) of a color chemist to respond to questions about specifications, color analysis, and color certification.

To expedite your response, I have already discussed these items with Dr. Flamm.

I would like to take this opportunity to give my warmest thanks to Jerry McCowin and Gene Coleman, and their fine staffs, and to Gary Flamm for his continued fine support. Please thank them for me--I know they have worked hard to assure that the panel has the materials necessary for their job.

Paul Lepore

May 24, 1985

Executive Secretary for Washington Operations

AGENDA - Fourth Panel Meeting

Members, Color Additive Scientific Review Panel

The fourth panel meeting will be held at 8:00 a.m. on May 31, 1985 in Room 14-63 of the Parklawn Building. Dr. Hart has prepared the following agenda:

1. Review, correcton and approval of the minutes of the third meeting.
2. Panel discussion with Dr. Franz.
3. Panel discussion with CFSAN Color Chemist.
4. A reading and discussion of the panelists' science reports.
5. A discussion of the format and contents of the panel's final report.
6. Plans.
7. Assignments

Paul Lepore

Panel Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

June 10, 1985

Executive Secretary

Minutes of the May 31st Meeting of the Color Additive
Scientific Review Panel

The Administrative Record

The fourth panel meeting was held to obtain clarification of the percutaneous studies and of the chemistry information, to develop a format for the panel's final report, and to otherwise continue the work of the panel. Dr. Freni served as the chair of the morning session and Dr. Hart (absent for the morning session) served as the chair for the afternoon session.

The minutes of the third panel meeting were accepted as written.

Dr. Franz (the scientist who performed the percutaneous absorption studies) was invited into the panel meeting at 8:57 a.m. He provided a background discussion on percutaneous absorption and he summarized his studies on the subject color additives. He then responded to the general and specific questions that were posed by the panelists. He stated that he would provide the panel with the references that indicate that facial skin is more permeable than abdominal skin and with the data sheets that present the radiochemical purity information for the colors issued in his studies (i.e., FD&C Red No. 3, and D&C Red No. 8 and 9). Dr. Franz was thanked for his help by Dr. Freni and he left the meeting at 11:15 a.m.

At 11:25 a.m., Mr. Keith Heine and Ms. Sandra Bell (Division of Color Technology, CFSAN), were invited into the meeting to discuss the chemistry aspects of the subject colors. The CFSAN scientists said that they would provide the panel with the additional chemical analyses that they had performed on the colors used in the animal studies, with the solubility data that they had, with the synthesis procedures used for D&C Red No. 19, and with information on the photodecomposition of the fluorosceines. The CFSAN scientists were thanked by Dr. Freni and they left the panel meeting at 12:15 p.m.

Dr. Hart assumed the chair for the afternoon session. The bulk of the discussion was devoted to the individual reports prepared by the panelists.

At this point, the panel developed a proposed format for the final report as follows:

I. Panel Concurrences
II. Executive Summary
III. Table of Contents
IV. Risk Assessments
V. Science Chapters
    A. Chemistry
    B. Metabolism

   C. Mutagenicity
   D. Bioassays
   E. Pathology
   F. Epidemiology
VI. Conclusions and Recommendations
VII. Appendices

Chairman Hart assigned the following action items:

- The panel is to finalize their chapters for the next meeting. Chairman Hart re-emphasized the goal to produce a report that contains the best scientific assessment of the available data and information.

- Panelists were urged to type their own reports on electronic media that could be transmitted to Arkansas. Dr. Turturro was to arrange for the typing of the final report.

The next panel meeting was set for 9:00 a.m. on June 7.

Paul Lepore

June 3, 1985

Executive Secretary for Washington Operations

AGENDA - Fifth Panel Meeting

Members, Color Additive Scientific Review Panel

The fifth panel meeting will be held at 9:00 a.m. on June 7, 1985 in Room 14-63 of the Parklawn Building. Dr. Hart has prepared the following agenda:

1. Review, correction and approval of the minutes of the fourth meeting.
2. Discussion of the final report.
3. Plans.
4. Assignments.

Paul Lepore

Panel Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

June 17, 1985

Executive Secretary

Minutes of the June 7th Meeting of the Color Additive
Scientific Review Panel

The Administrative Record

The fifth panel meeting was held to discuss the draft chapters in the panel's final report and to make plans for completing the final report. Drs. Freni and Gillette were not in attendance due to scheduling conflicts, however, they both arranged to submit to the panel drafts of their respective report chapters.

The minutes of the fourth panel meeting were revised and accepted.

Discussion was held on the format for the final report. The following format was generally accepted:

I. Panel Concurrences
II. Executive Summary
III. Table of Contents
IV. Introduction
V. Science Chapters
    A. Chemistry
    B. Metabolism
    C. Mutagenicity
    D. Bioassays and Pathology
VI. Risk Assessments
VII. Conclusions and Recommendations
VIII. Appendices

The Science Chapters were to include an introduction, background, color by color review, significance and references. The colors were to be discussed in the same order as that used by Dr. Freni in his draft report.

At this point, the panel discussed each of the chapters prepared by the individual members, sorted out the major issues, and attempted to reconcile these issues.

Chairman Hart assigned the following action items:

- The panel is to complete work on their chapters and send copies to Dr. Turturro.
- Dr. Turturro is to arrange for wordprocessing and editing of the report at NCTR.
- Dr. Lepore is to contact Dr. Franz to obtain copies of the specification sheet for radiolabeled Red No. 3 and of the literature references showing that facial skin is more permeable than abdominal skin. These are to be forwarded to Dr. Lowry.
- Dr. Lepore is to provide the report entry on Panel Concurrences.

The next meeting was scheduled for 10:00 a.m. on June 13 in a conference room that has speaker phone accommodation. The purpose of the meeting is to review the draft final report.

June 10, 1985

Executive Secretary for Washington Operations

AGENDA - Sixth Panel Meeting

Members, Color Additive Scientific Review Panel

The sixth panel meeting will be held at 10:00 a.m. on June 13, 1985 in Room 14-65 of the Parklawn Building. Dr. Hart has prepared the following agenda:

1. Review, correction and approval of the minutes of the fifth meeting.
2. Discussion of the final report.
3. Plans.
4. Assignments.

Paul Lepore

Panel Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

June 24, 1985

Executive Secretary

Minutes of the June 13th Meeting of the Color Additive
Scientific Review Panel

The Administrative Record

The sixth panel meeting was held to review the draft chapters of the final report and to continue the work of the panel. Drs. Freni and Ward were not in attendance due to scheduling conflicts. Their interests and concerns, however, were represented by Drs. Gaylor and Weisburger, respectively.

The minutes of the fifth panel meeting were revised and accepted.

As the panel reviewed the various draft chapters, it became apparent that the proposed format caused a good deal of redundancy. Accordingly, the panel agreed to revise the format to include an introduction containing information and assumptions common to all the colors and specific color chapters containing the science and risk assessment information for that color. Each of these chapters would contain a conclusion section so that there would be no need for the report to contain an overall summary and conclusions section.

Dr. Hart assigned the Executive Secretaries to edit the various chapters and to prepare a draft of the complete report including all appendices. The draft was then to be edited by Dr. Weisburger so that it could be available for comprehensive review at the next panel meeting.

The next panel meeting is scheduled for June 21st at 10:00 a.m.

Also scheduled is a status report for the Commissioner for June 28th at 2:30 p.m. in his conference room.

Paul Lepore

June 17, 1985

Executive Secretary for Washington Operations

AGENDA - Seventh Panel Meeting

Members, Color Additive Scientific Review Panel

The seventh panel meeting will be held at 10:00 a.m. on June 21, 1985 in Room 14-63 of the Parklawn Building. Dr. Hart has prepared the following agenda:

1. Review, correction and approval of the minutes of the sixth meeting.
2. Discussion of the final report.
3. Plans.
4. Assignments.

Paul Lepore

Panel Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

DRAFT

To: The Administrative Board

From: Executive Secretary

Subject: Minutes of the June 21st Meeting of the Color Additive Scientific Review Panel

The seventh panel meeting was held to continue work on the panel's final report. Dr. Freni was not in attendance but the Executive Secretary is keeping him informed via telecommunications.

The panel accepted the minutes of the sixth meeting and then proceeded to finalize the format of the report. This activity was followed by a page by page review so that consensus could be reached on each issue. NCTR was assigned the task of producing the report (graphics, binding, final typing).

The next meeting was scheduled for June 27th at 1:30 p.m. and June 28th at 9:00 a.m. The presentation for the Commissioner is scheduled for 2:30 p.m. in his conference room.

Paul Lepore

June 24, 1985

Executive Secretary for Washington Operations

AGENDA - Final Panel Meeting

Members, Color Additive Scientific Review Panel

The final panel meeting is scheduled for June 27th at 1:30 p.m. and June 29th at 9:00 a.m. in Room 14-63 of the Parklawn Building. The presentation for the Commissioner is scheduled for June 28th at 2:30 p.m. in his conference room.

The only agenda item is completion and presentation of the final report.

Paul Lepore

Panel Members
Dr. Hart
Dr. Freni
Dr. Gaylor
Dr. Gillette
Dr. Lowry
Dr. Ward
Dr. Weisburger

August 26, 1985

Executive Secretary

Minutes of the August 22 - 23 Meeting of the Color Additive Scientific
Review
Panel

The Administrative Record

The subject meeting was held to resolve the comments received from the external scientific reviewers of the draft panel report. Dr. Ward was not in attendance due to a scheduling conflict.

The meeting was facilitated by means of a "spread-sheet" which had categorized each of the issues raised in the comments into general and specific areas. The panel discussed each issue, arrived at a consensus, and modified the report as necessary. Plans were then agreed to on finalizing the report for presentation to the Commissioner.

Paul D. Lepore

cc:
Dr. Hart
Dr. Turturro
Dr. Freni
Dr. Weisburger
Dr. Ward
Dr. Gillette
Dr. Lowry
Dr. Gaylor

August 12, 1985

Executive Secretary for Washington Operations

Color Additive Scientific Review Panel Meeting

Panel Members

The next meeting of the Review Panel is scheduled for August 22 and 23, 1985, from 8:00 a.m. to 4:30 p.m. in conference room "O" of the Parklawn Building. The agenda will be the resolution of comments to the draft panel report.

Enclosed are the second set of responses (6) to the report on the Color Additive Scientific Review Panel for your review. As more responses are received in my office I will forward them to you.

Thank you for your cooperation.

Paul D. Lepore, Ph.D.

Enclosures

Appendix B - The bibliography used by the panel

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The CHAIRMAN. Well, I appreciate your analysis in terms of the risks. The concern is, if we continue the current practice, you are getting one result in terms of the risks and another kind of result in terms of benefits. We are really interested in understanding what the real health risks are.

Dr. YOUNG. I think that is correct.

The CHAIRMAN. And that is what I think our primary responsibility is.

I would be glad to hear from Mr. Parnell, and then I will recognize Senator Hatch.

Mr. PARNELL. Just briefly, to the extent that it might be able to clarify. I guess from USDA's point of view, we are really concerned that we are not so proscriptive in legislation that we will disallow a scientific decision to be made, and let me cite an example. There are certain fungicides used on a whole host of food products. They may, in fact, be determined to not meet the one in a million standard. If, in fact, that is the case, then if there are no alternatives, we would be exposing the American public to mycotoxins with which there are 14 that have been determined to be carcinogenic and even more onerous in terms of human health effects than whatever small residues may be left on food as it is consumed. So our concern is that we look at risk-risk, and I think much of the balancing that is done is focused on that area. What happens to the human health situation if we do not use some of these things? You can cite grain storage and a whole host of other positive that chemical development has given us the technology to reduce risk as a result of.

The CHAIRMAN. I will yield, but let me just say no one is trying to flyspeck the legislation. If you are talking about discretion to allow exceptional cases, you will not find any argument with me. But that really is not what the issue is.

Senator Hatch.

Senator HATCH. Well, thank you, Senator Kennedy. I appreciate that you called this particular hearing and are exploring this matter because I have had a tremendous interest in this area for many years. I have been arguing for years that we have to remove the Delaney clause and have a more scientific approach to ensure the safety of our food supply, among other things.

As I understand it, all three of you are in somewhat of an agreement in some areas, but all three of you disagree in other areas. For instance, FDA, it seems to me, supports the inerts testing in the Kennedy bill and makes the point that synergistic testing is unworkable. And that the negligible risk standard should be flexible, but it can be moved down? Is that a fair appraisal of what you said?

Dr. YOUNG. Yes, it is. And I think that negligible risk is absolutely just as you said, Senator, the heart of the issue.

Senator HATCH. Well, it really is. And the EPA seems to say we need to fix the negligible risk standard, but it should be a flexible standard. And then the USDA says there is no problem in our food supply and that pesticide residues are not adding cancer risks to our society; and, if I am not misstating it, the chemicals should be removed if they are proven unsafe, but that would be the case rather than proving them unsafe prior to use. Is that a fair statement?

Mr. **Parnell.** I think, Senator, in the process of registering, we do a couple of things, and a lot of the misunderstanding is borne out of the issue of using worst-case assumptions, extrapolations based on maximum allowable tolerances, as opposed to actual residue when the food is consumed. And I think there is a vast difference in our understanding there.

Senator **Hatch.** Well, Senator Kennedy's bill seems to go to a micro-risk problem rather than a macro-risk problem, to put it in economic terms. But, you see, what I am having trouble with—I do not want to take a lot of time here this morning because I have a lot of questions I could ask and take a lot of your time. But I am going to say this because you are my Administration, as far as I am concerned, but I think it is outrageous that after all these years of fighting this battle and looking at these issues, that the three most important agencies in Government come in here and are not together and that we do not speak with a unified voice. Now, I——

Mr. **Parnell.** Well, Senator Hatch, I think—and, again, I do not wish to be argumentative. I think we speak with a unified voice here today.

Senator **Hatch.** That is not the way I hear it, but I am glad to hear that.

Mr. **Parnell.** It may not be, but I think that we have had discussions prior, previous testimony at various times, and I do not think there is a vast amount of difference between EPA, FDA, and USDA's positions.

Senator **Hatch.** All right. Do you all want to come up with a reasonable, a decent negligible risk standard, or a de minims standard as we sometimes call it?

Mr. **Parnell.** If it is scientifically based.

Senator **Hatch.** Well, of course.

Mr. **Parnell.** And flexible, yes, sir.

Senator **Hatch.** I mean, when Delaney was instituted we could only measure parts per thousand. Now, we are measuring parts per trillion. We ought to go to a more scientific standard. And people do not seem to understand when you say a negligible risk standard that you are really going to create is a more accurate and safe analysis of our food than under the present system.

You had a comment, Doctor?

Dr. **Young.** Yes. I think that you are absolutely correct that it is important to have the act together for the Administration. As Mr. Parnell said, we have been meeting, and I think regretfully, as each of the oral testimonies were made, there was more of a focus on extraordinarily fine points than the uniform decision and agreement that a negligible risk standard is absolutely essential.

Senator **Hatch.** I am not going to take any more time other than to say this: I am disturbed that there is not a unified approach up here. Here we have Senator Kennedy and Congressman Waxman willing to do something in this area, albeit on a pesticide bill. Now, that is a nice start, but it really has to be much broader than a pesticide bill. And I happen to know that Senator Kennedy knows that. Frankly, I would like to see some resolution in this area.

You have an opportunity by coming here today to say: This is what ought to be done, and this will make our food supplies more safe; it will help to resolve the problems; it will be scientifically based; and we would like to see you do the following—and go far beyond the pesticides issue. That is important, but it is not the only area of importance with regard to food safety.

So I would challenge the three of you to get back with the Administration and sit down and come up with a unified approach here that has nothing to do with politics, and come up with an approach that we can then take. You have got people willing to work in a bipartisan way on this subject, without politics, for the benefit of the food supply of this country, among other things. And this is an opportunity that we have not had in the 10 years that I have been working on this. Frankly, you have got a good chairman in both areas, and I think you have got to lead in this area.

So I am challenging the three of you to get together with the Administration and come up with a unified approach that we can then implement into law. If we will do that, everybody is going to be better off. And I will tell you this: it would be landmark legislation. It would be some of the most important legislation in this country's history, and I think it is worth that kind of an effort. And I would like to see it done sooner than later.

Now, I was hoping it would be done for today.

Dr. YOUNG. Mr. Chairman, we can pledge to do that. We will be meeting, and we have agreed to meet as agencies together.

Senator HATCH. How long before we get a unified approach?

Dr. YOUNG. I think we can get you the unified approach in less than two months.

Senator HATCH. Oh, that is too long. You have had 10 years to look at this.

Dr. YOUNG. I said "less than."

Mr. KIMM. Now we are quibbling.

Senator HATCH. Oh, no, we are not. [Laughter.]

Dr. YOUNG. We will be meeting tomorrow in the first of our meetings as three agencies that will be moving around on this. We are focusing on this. EPA has the lead to look at the negligible risk standard. We are working on this at the moment. I think possibly the disarray was more apparent than real because what I think unfortunately happened is each witness was focusing on some of the minor points. As I mentioned in my opening statement, I strongly support this approach. I think that negligible risk is the absolute correct way to go. I think it is the right thing for the American people. We have to distinguish between real and imagined risks, and unless we can do that, we fail.

Senator HATCH. Well, I think we are making headway.

If you would, the three of you, just chat for a minute about enforcement and what needs to be done there.

Dr. YOUNG. I think one of the most fundamental things that we need to do is bring the enforcement up to a level, Senator Hatch, that is really visible enough so that the American people have confidence in it. Therefore, we will be recommending through some sort of a mechanism that there is an increase in the enforcement action so that the people can have confidence that once the tolerance is set that that will be in place.

Senator Hatch. Well, I will not take any more time. Let me just say this: I understand that you have three different approaches and views with regard to enforcement. The reason I raised it is I would like you to get together on enforcement as well. If you are not together, get together.

Dr. Young. We are together on enforcement, at this point.

Senator Hatch. I am talking about how to accomplish enforcement.

Dr. Young. I think we are pretty much together on this now. We were not a little while ago, but we have been hammering some things out.

Senator Hatch. All right. I would like to have this back within a month, certainly before we go to the August recess. You might look at some of the work that this committee did in the past with regard to food safety and some of the legislation that was promulgated at that time, and go beyond that and benefit from the intervening years and come up with something that really everybody can support.

Dr. Young. I think we can meet that one-month deadline.

The Chairman. Good. Excellent.

Senator Hatch. You and I are certainly interested in that.

The Chairman. Yes.

Senator Hatch. And I think everybody else in this committee is as well, and I think Henry Waxman and Ed Madigan and John Dingell, et al., over there will be interested. This is the year to do this. And if we could do this, it would be a tremendous, tremendous thing to do for our country.

Well, I will not take any more time.

Dr. Young. Thank you.

The Chairman. Thank you very much. Senator Harkin.

Senator Harkin. Thank you very much, Mr. Chairman. I would just like to ask that my statement be made a part of the record.

The Chairman. It will be made a part of the record.

[The prepared statement of Senator Harkin follows:]

PREPARED STATEMENT OF SENATOR HARKIN

Mr. Chairman, thank you for holding this hearing today on the Food Safety Amendments of 1989. Recent public attention to the safety of our Nation's food supply requires that we closely examine environmental and human health effects of pesticides and the way we regulate them. I want to thank all the witnesses for coming today and I look forward to hearing their testimony.

I think we all agree the paramount issue is consumer food safety. As a Senator from an agricultural state, I can assure you that farmers want to produce safe food. They want assurances that they are using safe practices, and the American food supply is the safest in the world. But, we have an obligation to help make it safer where we can do that within reason.

There is fair agreement that the confidence of Americans in the safety of our food supply has suffered. This is bad for consumers and for agriculture. Consumers are receiving confusing information about what is safe and what is potentially dangerous, as was highlighted by the recent attention to daminozide, or ALAR, where the Food and Drug Administration (FDA) and the U.S. Department of Agriculture were saying that apples are safe, while the Environmental Protection Agency (EPA) was moving to cancel its use. What does this do to consumer confidence? Our agricultural producers cannot stand one food scare after another. We must find a way to rebuild consumer confidence on a solid scientific base.

A point too often overlooked is that farmers are vitally interested in pesticide safety issues. They raise their children, breathe the air and drink the water in farming area where the pesticides are used. And, farm families are consumers too. Farmers want to know that the pesticides that they use are safe for consumers and for themselves and their families. But they also want to remain in business and be efficient producers.

As a Senator from one of our nation's leading agricultural states, I know that pesticides have become an integral part of modern farming. Pesticides help farmers produce the abundant quantities of low-cost food that our consumers have become accustomed to. It is not reasonable to think that our farmers will be able to, or need to, abandon using pesticides in the foreseeable future. And when properly used, pesticides do not, by and large, pose unreasonable risks to consumers.

There are encouraging developments. More and more farmers are using smaller amounts of pesticides and newer, safer pesticides. This makes good economic sense in addition to reducing the risk to the environment and human health. Biotechnology could drastically reduce the need for pesticides. These new methods and technologies deserve research and encouragement. But at the present time, the most effective way to reduce risk is to make sure the pesticides in use are safe—judged by reasonable standards—and that they are used properly and carefully.

As we strive to ensure pesticide safety, we face some serious problems in pesticide regulation that have been highlighted by the recent attention to daminozide, or ALAR. In short, resolving questions about the safety of certain pesticides has taken too long. This delay, and the twists and turns of the regulatory path, have in turn, severely undermined consumer confidence in the food supply and in the pesticide regulators. This confidence must be rebuilt on a solid base, based on a rational approach involving scientific principles, for the good of consumers and the agricultural sector alike. Consumers will not be satisfied with bland assurances, they will demand that any assertions be backed by credible science.

Mr. Chairman, I look forward to working with you in clarifying the issues and determining the possible problems and their solutions on these important matters.

Senator HATCH. May I submit additional questions?

The CHAIRMAN. Yes. We will all be able to have additional questions.

Senator HARKIN. I think enough has been said about the conflicts. I do not want to go into that. But I think it does say something about consumer fears when they find that the USDA and FDA were telling the public that the apples were safe in the ALAR scare, and EPA was moving to cancel the use of ALAR. What do people think when they see that kind of a conflict. I think that has been talked about enough here.

What I would like to focus on has to do with evaluating the pesticides, fungicides, herbicides on a worst-case basis. Now, looking ahead at some of the testimony to be presented later by the National Academy of Sciences, they say that residues of a dozen or so pesticides in or on 15 or 20 crops accounted for at least 90 percent of the total estimated worst-case risk. Does that ring a bell with any of you?

Dr. YOUNG. Yes, sir.

Mr. KIMM. Yes.

Senator HARKIN. You say yes; you, Mr. Parnell, say no.

Mr. PARNELL. Well, I am familiar with the report. I am talking about actual residue samplings. It does not seem to bear that out.

Dr. YOUNG. You are correct that that is in the report.

Senator HARKIN. That is in the report.

Dr. YOUNG. Absolutely.

Senator HARKIN. This is a book that they put out a couple of years ago.

Dr. YOUNG. I am very familiar with that.

Senator HARKIN. Has this got good scientific basis?

Dr. **Young**. It has a good scientific analysis. It was done more as an armchair analysis rather than a complete laboratory approach. But, yes, it is a credible analysis.

Senator **Harkin**. I do not know what an armchair approach is. What does that mean?

Dr. **Young**. It was not done in a laboratory where these were tested individually. It was done by inspection of the data and the best estimate possible.

Mr. **Parnell**. It was using worst-case scenario information.

Mr. **Kimm**. In the particular array of where the biggest risks were, there were some assumptions in the absence of measured data about the level of pesticide that might be present on the residue and the numbers of pesticides that might be applied to a particular crop. Earlier, Dr. Young made the comment about a hundred pesticides that might be used on apples. Well, it is very, very unlikely you are ever going to find one that had more than a few pesticides used on it. So to the degree that those numbers were based on theoretical calculations, they overstate the risk. To the degree that they say, however, that these are where the high risks are likely to be, we share that view and have, in fact, been pursuing regulatory strategies to look at those pesticides first.

Senator **Harkin**. OK. Well, on page 68 of the report, they have a table here, and they have estimated oncogenic risk from dietary exposure to 28 pesticides. They just took 28.

Dr. **Young**. That is correct.

Senator **Harkin**. Well, there is a whole list here. I put a cut-off line where the one in a million would fall, and it is about—I did not count them, but I would say it looks like about 18. Then when I see the year of first tolerance, these are all old ones: 1966, 1955, 1959—there is one, 1978, that is the latest one—1955, 1972, 1961, 1955 again. These are all things that have not really been reviewed, have they?

Dr. **Young**. That is correct, and that is one of the issues that your bill speaks to in regard to how to update these. It is also appropriate to say that the analysis on which these are based are the classical and appropriate risk analyses which give you the maximum risk, and that is what you go from, yes.

Senator **Harkin**. Well, what I would like to know, my baseline question is this: Have you done any kind of an assessment on the impact on agriculture if you would just ban those that are the most highest risk? Again, I am just taking the National Academy's statement here saying that over 90 percent of the worst-case dietary risk came from just a dozen or so pesticides. Have you done any analysis of the impact on agriculture if you just do away with those?

Mr. **Kimm**. You have got a very complicated problem, Senator, and you have got a very simple solution to it—but it does not work, that is the problem. The actual risks associated with those pesticides are all smaller than on that table, and we know that because, again, as I said earlier, everything is not used that could be used on any individual crops, and everything is not treated up to the level of the tolerance, and no human being gets food at the level of the tolerance for their entire lifetime. So the risks you are looking at all overstate the risk. They are relative; they give you some idea where the more risky things are; they are good for setting priorities. But in terms of numbers of our best guess of the real risks, they are not appropriate.

Now, we take the chemicals on in groups or individually, and we perform fairly detailed analysis in something we call special review where we try to look at the risks as best we understand them. We often try to get better residue data so we have a better understanding of the actual exposure to people, and that is how we set the framework for our regulatory activities. But it is not, unfortunately, a simple matter of saying: Take the top 15, cross them off, and there is no problem left. It just is not like that, Senator.

Senator HARKIN. These things have been under review for, what, over 20 years now? These fungicides and stuff have been under review for about 20 years? What I am trying to ask is, what work is being done on alternatives? They keep reviewing these; they keep beating these around. What work is really being done on finding alternatives to this?

Mr. PARNELL. Well, we spend a considerable amount of time and effort on alternatives in terms of integrated pest management, biological controls. I think biotechnology will offer some solutions, but science is moving as fast as it can in that regard. Quite honestly, we just do not have all of those answers. I think as we walk into the future, and the rather immediate future, we will be seeing as a result of some of the technology that is being developed a significant reduction in the amount of the chemicals utilized. But, clearly, today we are not absolutely there. We are working to get there.

Dr. YOUNG. Senator, I would like to address your question as a scientist. FDA does not have the responsibility for doing these risk assessments. That is something that EPA does. But, scientifically speaking, I believe your question demands an answer. It is just what Senator Hatch focused on as well. We need to, as a society, be able to get a consensus on risk assessment. The difference that I developed there was that these were estimates. What I meant by armchair was look at the data, determine the best estimates. What Victor Kimm is emphasizing is you really need to take these leads—and I think those are important leads to look at—and go in detail on each of these.

I provided for the record, and I mentioned in my opening statement, that there could be a hundred pesticides used on apples alone. Not all of those are used. So when you come up with these types of assessments, I believe it demands taking a good model approach, take the most significant one, and go down in detail, analyze that, get it peer reviewed, and then discuss that with the public. Until we do that, as Senator Hatch challenged us, we will be failing because we will have not developed a consensus. And I believe that is what we are looking forward to doing and trying to work with the Academy and other organizations, to determine the difference between real and imagined risks.

Bruce Ames in a scientific article which I will submit also focused on the need to look at natural versus artificial carcinogens.

[The articles referred to follow:]

Extra Cop.

Ranking Possible Carcinogenic Hazards

Bruce N. Ames,* Renae Magaw, Lois Swirsky Gold

This review discusses reasons why animal cancer tests cannot be used to predict absolute human risks. Such tests, however, may be used to indicate that some chemicals might be of greater concern than others. Possible hazards to humans from a variety of rodent carcinogens are ranked by an index that relates the potency of each carcinogen in rodents to the exposure in humans. This ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances, though one cannot say whether these natural exposures are likely to be of major or minor importance.

EPIDEMIOLOGISTS ESTIMATE THAT AT LEAST 70% OF HUMAN cancer would, in principle, be preventable if the main risk and antirisk factors could be identified (*1*). This is because the incidence of specific types of cancer differs markedly in different parts of the world where people have different life-styles. For example, colon and breast cancer, which are among the major types of cancer in the United States, are quite rare among Japanese in Japan, but not among Japanese-Americans. Epidemiologists are providing important clues about the specific causes of human cancer, despite inherent methodological difficulties. They have identified tobacco as an avoidable cause of about 30% of all U.S. cancer deaths and of an even larger number of deaths from other causes (*1*, *2*). Less specifically, dietary factors, or their absence, have been suggested in many studies to contribute to a substantial proportion of cancer deaths, though the intertwined risk and antirisk factors are being identified only slowly (*1*, *3*, *4*). High fat intake may be a major contributor to colon cancer, though the evidence is not as definitive as that for the role of saturated fat in heart disease or of tobacco in lung cancer. Alcoholic beverage consumption, particularly by smokers, has been estimated to contribute to about 3% of U.S. cancer deaths (*1*) and to an even larger number of deaths from other causes. Progress in prevention has been made for some occupational factors, such as asbestos, to which workers used to be heavily exposed, with delayed effects that still contribute to about 2% of U.S. cancer deaths (*1*, *5*). Prevention may also become possible for hormone-related cancers such as breast cancer (*1*, *6*), or virus-related cancers such as liver cancer (hepatitis B) and cancer of the cervix (papilloma virus HPV16) (*1*, *7*).

Animal bioassays and in vitro studies are also providing clues as to which carcinogens and mutagens might be contributing to human cancer. However, the evaluation of carcinogenicity in rodents is expensive and the extrapolation to humans is difficult (*8*–*11*). We will use the term "possible hazard" for estimates based on rodent cancer tests and "risk" for those based on human cancer data (*10*).

Extrapolation from the results of rodent cancer tests done at high doses to effects on humans exposed to low doses is routinely attempted by regulatory agencies when formulating policies attempting to prevent future cancer. There is little sound scientific basis for this type of extrapolation, in part due to our lack of knowledge about mechanisms of cancer induction, and it is viewed with great unease by many epidemiologists and toxicologists (*5*, *9*–*11*). Nevertheless, to be prudent in regulatory policy, and in the absence of good human data (almost always the case), some reliance on animal cancer tests is unavoidable. The best use of them should be made even though few, if any, of the main avoidable causes of human cancer have typically been the types of man-made chemicals that are being tested in animals (*10*). Human cancer may, in part, involve agents such as hepatitis B virus, which causes chronic inflammation; changes in hormonal status; deficiencies in normal protective factors (such as selenium or β-carotene) against endogenous carcinogens (*12*); lack of other anticarcinogens (such as dietary fiber or calcium) (*4*); or dietary imbalances such as excess consumption of fat (*3*, *4*, *12*) or salt (*13*).

There is a need for more balance in animal cancer testing to emphasize the foregoing factors and natural chemicals as well as synthetic chemicals (*12*). There is increasing evidence that our normal diet contains many rodent carcinogens, all perfectly natural or traditional (for example, from the cooking of food) (*12*), and that no human diet can be entirely free of mutagens or agents that can be carcinogenic in rodent systems. We need to identify the important causes of human cancer among the vast number of minimal risks. This requires knowledge of both the amount of a substance to which humans are exposed and its carcinogenic potency.

Animal cancer tests can be analyzed quantitatively to give an estimate of the relative carcinogenic potencies of the chemicals tested. We have previously published our Carcinogenic Potency Database, which showed that rodent carcinogens vary in potency by more than 10 millionfold (*14*).

This article attempts to achieve some perspective on the plethora of possible hazards to humans from exposure to known rodent carcinogens by establishing a scale of the possible hazards for the amounts of various common carcinogens to which humans might be chronically exposed. We view the value of our calculations not as providing a basis for absolute human risk assessment, but as a guide to priority setting. One problem with this type of analysis is that few of the many natural chemicals we are exposed to in very large amounts (relative to synthetic chemicals) have been tested in animals for carcinogenicity. Thus, our knowledge of the background levels of human exposure to animal carcinogens is fragmentary, biased in favor of synthetic chemicals, and limited by our lack of knowledge of human exposures.

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Ranking of Possible Carcinogenic Hazards

Since carcinogens differ enormously in potency, a comparison of possible hazards from various carcinogens ingested by humans must take this into account. The measure of potency that we have developed, the TD$_{50}$, is the daily dose rate (in milligrams per kilogram) to halve the percent of tumor-free animals by the end of a standard lifetime (14). Since the TD$_{50}$ (analogous to the LD$_{50}$) is a dose rate, the lower the TD$_{50}$ value the more potent the carcinogen. To calculate our index of possible hazard we express each human exposure (daily lifetime dose in milligrams per kilogram) as a percentage of the rodent TD$_{50}$ dose (in milligrams per kilogram) for each carcinogen. We call this percentage HERP [*Human Exposure dose/Rodent Potency dose*]. The TD$_{50}$ values are taken from our ongoing Carcinogenic Potency Database (currently 3500 experiments on 975 chemicals), which reports the TD$_{50}$ values estimated from experiments in animals (14). Human exposures have been estimated from the literature as indicated. As rodent data are all calculated on the basis of lifetime exposure at the indicated daily dose rate (14), the human exposure data are similarly expressed as lifelong daily dose rates even though the human exposure is likely to be less than daily for a lifetime.

It would be a mistake to use our HERP index as a direct estimate of human hazard. First, at low dose rates human susceptibility may differ systematically from rodent susceptibility. Second, the general shape of the dose-response relationship is not known. A linear dose response has been the dominant assumption in regulating carcinogens for many years, but this may not be correct. If the dose responses are not linear but are actually quadratic or hockey-stick shaped or show a threshold, then the actual hazard at low dose rates might be much less than the HERP values would suggest. An additional difficulty is that it may be necessary to deal with rcinogens that differ in their mechanisms of action and thus in eir dose-response relationship. We have therefore put an asterisk next to HERP values for carcinogens that do not appear to be active through a genotoxic (DNA damaging or mutagenic) mechanism (15) so that comparisons can be made within the genotoxic or nongenotoxic classes.

Table 1 presents our HERP calculations of possible cancer hazards in order to compare them within several categories so that, for example, pollutants of possible concern can be compared to natural carcinogens in the diet. A convenient reference point is the possible hazard from the carcinogen chloroform in a liter of average (U.S.) chlorinated tap water, which is close to a HERP of 0.001%. Chloroform is a by-product of water chlorination, which protects us from pathogenic viruses and bacteria.

Contaminated water. The possible hazards from carcinogens in contaminated well water [for example, Santa Clara ("Silicon") Valley, California, or Woburn, Massachusetts] should be compared to the possible hazard of ordinary tap water (Table 1). Of 35 wells shut down in Santa Clara Valley because of their supposed carcinogenic hazard, only two have HERP values greater than ordinary tap water. Well water is not usually chlorinated and typically lacks the chloroform present in chlorinated tap water. Water from the most polluted well (HERP = 0.004% per liter for trichloroethylene), as indicated in Table 1, has a HERP value orders of magnitude less than for the carcinogens in an equal volume of cola, beer, or wine. Its HERP value is also much lower than that of many of the common natural foods that are listed in Table 1, such as the average nut butter sandwich. Caveats for any comparisons are given ow. Since the consumption of tap water is only about 1 or 2 liters per day, the animal evidence provides no good reason to expect that chlorination of water or current levels of man-made pollution of water pose a significant carcinogenic hazard.

Pesticide residues. Intake of man-made pesticide residues from food in the United States, including residues of industrial chemicals such as polychlorinated biphenyls (PCBs), averages about 150 μg/day. Most (105 μg) of this intake is composed of three chemicals (ethylhexyl diphenyl phosphate, malathion, and chlorpropham) shown to be noncarcinogenic in tests in rodents (16). A carcinogenic pesticide residue in food of possible concern is DDE, the principal metabolite (>90%) of DDT (16). The average U.S. daily intake of DDE from DDT (HERP = 0.0003%) is equivalent to the HERP of the chloroform in one glass of tap water and thus appears to be insignificant compared to the background of natural carcinogens in our diet (Table 1). Even daily consumption of 100 times the average intake of DDE/DDT or PCBs would produce a possible hazard that is small compared to other common exposures shown in Table 1.

Nature's pesticides. We are ingesting in our diet at least 10,000 times more by weight of natural pesticides than of man-made pesticide residues (12). These are natural "toxic chemicals" that have an enormous variety of chemical structures, appear to be present in all plants, and serve to protect plants against fungi, insects, and animal predators (12). Though only a few are present in each plant species, they commonly make up 5 to 10% of the plant's dry weight (12). There has been relatively little interest in the toxicology or carcinogenicity of these compounds until quite recently, although they are by far the main source of "toxic chemicals" ingested by humans. Only a few dozen of the thousands present in the human diet have been tested in animal bioassays, and only some of these tests are adequate for estimating potency in rodents (14). A sizable proportion of those that have been tested are carcinogens, and many others have been shown to be mutagens (12), so it is probable that many more will be found to be carcinogens if tested. Those shown in Table 1 are: estragole (HERP = 0.1% for a daily 1 g of dried basil), safrole (HERP = 0.2% for a daily natural root beer), symphytine (a pyrrolizidine alkaloid, 0.03% for a daily cup of comfrey tea), comfrey tablets sold in health food stores (6.2% for a daily dose), hydrazines in mushrooms (0.1% for one daily raw mushroom), and allyl isothiocyanate (0.07% for a daily 5 g of brown mustard).

Plants commonly produce very much larger amounts of their natural toxins when damaged by insects or fungi (12). For example, psoralens, light-activated carcinogens in celery, increase 100-fold when the plants are damaged by mold and, in fact, can cause an occupational disease in celery-pickers and in produce-checkers at supermarkets (12, 17).

Molds synthesize a wide variety of toxins, apparently as antibiotics in the microbiological struggle for survival: over 300 mycotoxins have been described (18). They are common pollutants of human food, particularly in the tropics. A considerable percentage of those tested have been shown to be mutagens and carcinogens: some, such as aflatoxin and sterigmatocystin, are among the most potent known rodent carcinogens. The potency of aflatoxin in different species varies widely; thus, a bias may exist as the HERP uses the most sensitive species. The aflatoxin content of U.S. peanut butter averages 2 ppb, which corresponds to a HERP of 0.03% for the peanut butter in an average sandwich (Table 1). The Food and Drug Administration (FDA) allows ten times this level (HERP = 0.3%), and certain foods can often exceed the allowable limit (18). Aflatoxin contaminates wheat, corn (perhaps the main source of dietary aflatoxin in the United States), and nuts, as well as a wide variety of stored carbohydrate foodstuffs. A carcinogenic, though less potent, metabolite of aflatoxin is found in milk from cows that eat moldy grain.

There is epidemiologic evidence that aflatoxin is a human carcinogen. High intake in the tropics is associated with a high rate of liver cancer, at least among those chronically infected with the hepatitis B ture (19, 20). Considering the potency of those mold toxins that have been tested and the widespread contamination of food with molds, they may represent the most significant carcinogenic pollution of the food supply in developing countries. Such pollution is much less severe in industrialized countries, due to refrigeration and modern techniques of agriculture and storage, including use of synthetic pesticides and fumigants.

Preparation of foods and beverages can also produce carcinogens. Alcohol has been shown to be a human carcinogen in numerous epidemiologic studies (*1*, *21*). Both alcohol and acetaldehyde, its

Table 1. Ranking possible carcinogenic hazards. *Potency of carcinogens*: A number in parentheses indicates a TD_{50} value not used in HERP calculation because it is the less sensitive species; (−) = negative in cancer test. (+) = positive for carcinogenicity in test(s) not suitable for calculating a TD_{50}; (?) = is not adequately tested for carcinogenicity. TD_{50} values shown are averages calculated by taking the harmonic mean of the TD_{50}'s of the positive tests in that species from the Carcinogenic Potency Database. Results are similar if the lowest TD_{50} value (most potent) is used instead. For each test the target site with the lowest TD_{50} value has been used. The average TD_{50} has been calculated separately for rats and mice, and the more sensitive species is used for calculating the possible hazard. The database, with references to the source of the cancer tests, is complete for tests published through 1984 and for the National Toxicology Program bioassays through June 1986 (*14*). We have not indicated the route of exposure or target sites or other particulars of each test, although these are reported in the database. *Daily human exposure*: We have tried to use average or reasonable daily intakes to facilitate comparisons. In several cases, such as contaminated well water or factory exposure to EDB, this is difficult to determine, and we give the value for the worst found and indicate pertinent information in the References and Notes. The calculations assume a daily dose for a lifetime; where drugs are normally taken for only a short period we have bracketed the HERP value. For inhalation exposures we assume an inhalation of 9,600 liters per 8 hours for the workplace and 10,800 liters per 14 hours for indoor air at home. *Possible hazard*: The amount of rodent carcinogen indicated under carcinogen dose is divided by 70 kg to give a milligram per kilogram of human exposure, and this human dose is given as the percentage of the TD_{50} dose in the rodent (in milligrams per kilogram) to calculate the *Human Exposure/Rodent Potency index* (HERP).

Possible hazard: HERP (%)	Daily human exposure	Carcinogen dose per 70-kg person	Potency of carcinogen: TD_{50} (mg/kg)		References
			Rats	Mice	
		Environmental pollution			
0.001*	Tap water, 1 liter	Chloroform, 83 μg (U.S. average)	(119)	90	*96*
0.004*	Well water, 1 liter contaminated (worst well in Silicon Valley)	Trichloroethylene, 2800 μg	(−)	941	*97*
0.0004*	Well water, 1 liter contaminated, Woburn	Trichloroethylene, 267 μg	(−)	941	*98*
0.0002*		Chloroform, 12 μg	(119)	90	
0.0003*		Tetrachloroethylene, 21 μg	101	(126)	
0.008*	Swimming pool, 1 hour (for child)	Chloroform, 250 μg (average pool)	(119)	90	*99*
0.6	Conventional home air (14 hour/day)	Formaldehyde, 598 μg	1.5	(44)	*100*
0.004		Benzene, 155 μg	(157)	53	
2.1	Mobile home air (14 hour/day)	Formaldehyde, 2.2 mg	1.5	(44)	*28*
		Pesticide and other residues			
0.0002*	PCBs: daily dietary intake	PCBs, 0.2 μg (U.S. average)	1.7	(9.6)	*101*
0.0003*	DDE/DDT: daily dietary intake	DDE, 2.2 μg (U.S. average)	(−)	13	*16*
0.0004	EDB: daily dietary intake (from grains and grain products)	Ethylene dibromide, 0.42 μg (U.S. average)	1.5	(5.1)	*102*
		Natural pesticides and dietary toxins			
0.003	Bacon, cooked (100 g)	Dimethylnitrosamine, 0.3 μg	(0.2)	0.2	*40*
0.006		Diethylnitrosamine, 0.1 μg	0.02	(+)	
0.003	Sake (250 ml)	Urethane, 43 μg	(41)	22	*34*
0.03	Comfrey herb tea, 1 cup	Symphytine, 38 μg (750 μg of pyrrolizidine alkaloids)	1.9	(?)	*103*
0.03	Peanut butter (32 g; one sandwich)	Aflatoxin, 64 ng (U.S. average, 2 ppb)	0.003	(+)	*18*
0.06	Dried squid, broiled in gas oven (54 g)	Dimethylnitrosamine, 7.9 μg	(0.2)	0.2	*37*
0.07	Brown mustard (5 g)	Allyl isothiocyanate, 4.6 mg	96	(−)	*47*
0.1	Basil (1 g of dried leaf)	Estragole, 3.8 mg	(?)	52	*48*
0.1	Mushroom, one raw (15 g) (*Agaricus bisporus*)	Mixture of hydrazines, and so forth	(?)	20,300	*104*
0.2	Natural root beer (12 ounces; 354 ml) (now banned)	Safrole, 6.6 mg	(436)	56	*105*
0.008	Beer, before 1979 (12 ounces; 354 ml)	Dimethylnitrosamine, 1 μg	(0.2)	0.2	*38*
2.8*	Beer (12 ounces; 354 ml)	Ethyl alcohol, 18 ml	9110	(?)	*23*
4.7*	Wine (250 ml)	Ethyl alcohol, 30 ml	9110	(?)	*23*
6.2	Comfrey-pepsin tablets (nine daily)	Comfrey root, 2700 mg	626	(?)	*103*
1.3	Comfrey-pepsin tablets (nine daily)	Symphytine, 1.8 mg	1.9	(?)	
		Food additives			
0.0002	AF-2: daily dietary intake before banning	AF-2 (furylfuramide), 4.8 μg	29	(131)	*44*
0.06*	Diet Cola (12 ounces; 354 ml)	Saccharin, 95 mg	2143	(−)	*106*
		Drugs			
[0.3]	Phenacetin pill (average dose)	Phenacetin, 300 mg	1246	(2137)	*51*
[5.6]	Metronidazole (therapeutic dose)	Metronidazole, 2000 mg	(542)	506	*107*
[14]	Isoniazid pill (prophylactic dose)	Isoniazid, 300 mg	(150)	30	*108*
16*	Phenobarbital, one sleeping pill	Phenobarbital, 60 mg	(+)	5.5	*50*
17*	Clofibrate (average daily dose)	Clofibrate, 2000 mg	169	(?)	*52*
		Occupational exposure			
5.8	Formaldehyde: Workers' average daily intake	Formaldehyde, 6.1 mg	1.5	(44)	*109*
140	EDB: Workers' daily intake (high exposure)	Ethylene dibromide, 150 mg	1.5	(5.1)	*55*

*Asterisk indicates HERP from carcinogens thought to be nongenotoxic.

major metabolite, are carcinogens in rats (*22, 23*). The carcinogenic potency of ethyl alcohol in rats is remarkably low (*23*), and it is among the weakest carcinogens in our database. However, human intake of alcohol is very high (about 18 g per beer), so that the possible hazards shown in Table 1 for beer and wine are large (HERP = 2.8% for a daily beer). The possible hazard of alcohol is enormous relative to that from the intake of synthetic chemical residues. If alcohol (*20*), trichloroethylene, DDT, and other presumptive nongenotoxic carcinogens are active at high doses because they are tumor promoters, the risk from low doses may be minimal.

Other carcinogens are present in beverages and prepared foods. Urethane (ethyl carbamate), a particularly well-studied rodent carcinogen, is formed from ethyl alcohol and carbamyl phosphate during a variety of fermentations and is present in Japanese sake (HERP = 0.003%), many types of wine and beer, and in smaller amounts in yogurt and bread (*24*). Another fermentation product, the dicarbonyl aldehyde methylglyoxal, is a potent mutagen and was isolated as the main mutagen in coffee (about 250 μg in one cup). It was recently shown to be a carcinogen, though not in a test suitable for calculating a TD_{50} (*25*). *Methylglyoxal* is also present in a variety of other foods, such as tomato puree (*25, 26*). Diacetyl (2,3-butanedione), a closely related dicarbonyl compound, is a fermentation product in wine and a number of other foods and is responsible for the aroma of butter. Diacetyl is a mutagen (*27*) but has not been tested for carcinogenicity.

Formaldehyde, another natural carcinogenic and mutagenic aldehyde, is also present in many common foods (*22, 26–28*). Formaldehyde gas caused cancer only in the nasal turbinates of the nose-breathing rodents and even though formaldehyde is genotoxic, the dose response was nonlinear (*28, 29*). Hexamethylenetetramine, which decomposes to formaldehyde in the stomach, was negative in feeding studies (*30*). The effects of oral versus inhalation exposure formaldehyde remain to be evaluated more thoroughly.

As formaldehyde is almost ubiquitous in foods, one can visualize various formaldehyde-rich scenarios. Daily consumption of shrimp (HERP = 0.09% per 100 g) (*31*), a sandwich (HERP of two slices of bread = 0.4%) (*22*), a cola (HERP = 2.7%) (*32*), and a beer (HERP = 0.2%) (*32*) in various combinations could provide as much formaldehyde as living in some mobile homes (HERP = 2.1%; Table 1). Formaldehyde is also generated in animals metabolically, for example, from methoxy compounds that humans ingest in considerable amounts from plants. The level of formaldehyde reported in normal human blood is strikingly high (about 100 μ*M* or 3000 ppb) (*33*) suggesting that detoxification mechanisms are important.

The cooking of food generates a variety of mutagens and carcinogens. Nine heterocyclic amines, isolated on the basis of their mutagenicity from proteins or amino acids that were heated in ways that occur in cooking, have now been tested; all have been shown to be potent carcinogens in rodents (*34*). Many others are still being isolated and characterized (*34*). An approximate HERP of 0.02% has been calculated by Sugimura *et al.* for the daily intake of these nine carcinogens (*34*). Three mutagenic nitropyrenes present in diesel exhaust have now been shown to be carcinogens (*35*), but the intake of these carcinogenic nitropyrenes has been estimated to be much higher from grilled chicken than from air pollution (*34, 36*). The total amount of browned and burnt material eaten in a typical day is at least several hundred times more than that inhaled from severe air pollution (*12*).

Gas flames generate NO_2, which can form both the carcinogenic nitropyrenes (*35, 36*) and the potently carcinogenic nitrosamines in food cooked in gas ovens, such as fish or squid (HERP = 0.06%; Table 1) (*37*). We suspect that food cooked in gas ovens may be a major source of dietary nitrosamines and nitropyrenes, though it is not clear how significant a risk these pose. Nitrosamines were ubiquitous in beer and ale (HERP = 0.008%) and were formed from NO_2 in the gas flame–heated air used to dry the malt. However, the industry has switched to indirect heating, which resulted in markedly lower levels (<1 ppb) of dimethylnitrosamine (*38*). The dimethylnitrosamine found in human urine is thought to be formed in part from NO_2 inhaled from kitchen air (*39*). Cooked bacon contains several nitrosamines (HERP = 0.009%) (*40*).

Oxidation of fats and vegetable oils occurs during cooking and also spontaneously if antioxidant levels are low. The result is the formation of peroxides, epoxides, and aldehydes, all of which appear to be rodent carcinogens (*8, 12, 27*). Fatty acid hydroperoxides (present in oxidized oils) and cholesterol epoxide have been shown to be rodent carcinogens (though not in tests suitable for calculating a TD_{50}). Dried eggs contain about 25 ppm of cholesterol epoxide (a sizable amount), a result of the oxidation of cholesterol by the NO_2 in the drying air that is warmed by gas flames (*12*).

Normal oxidation reactions in fruit (such as browning in a cut apple) also involve production of peroxides. Hydrogen peroxide is a mutagenic rodent carcinogen that is generated by oxidation of natural phenolic compounds that are quite widespread in edible plants. A cup of coffee contains about 750 μg of hydrogen peroxide (*25*); however, since hydrogen peroxide is a very weak carcinogen (similar in potency to alcohol), the HERP for drinking a daily cup of coffee would be very low [comparable to DDE/DDT, PCBs, or ethylene dibromide (EDB) dietary intakes]. Hydrogen peroxide is also generated in our normal metabolism; human blood contains about 5 μ*M* hydrogen peroxide and 0.3 μ*M* of the cholesterol ester of fatty acid hydroperoxide (*41*). Endogenous oxidants such as hydrogen peroxide may make a major contribution to cancer and aging (*42*).

Caloric intake, which could be considered the most striking rodent carcinogen ever discovered, is discussed remarkably little in relation to human cancer. It has been known for about 40 years that increasing the food intake in rats and mice by about 20% above optimal causes a remarkable decrease in longevity and a striking increase in endocrine and mammary tumors (*43*). In humans, obesity (associated with high caloric intake) leads to increased levels of circulating estrogens, a significant cause of endometrial and gall bladder cancer. The effects of moderate obesity on other types of human cancer are less clear (*1*).

Food additives are currently screened for carcinogenicity before use if they are synthetic compounds. AF-2 (HERP = 0.0002%), a food preservative, was banned in Japan (*44*). Saccharin (HERP = 0.06%) is currently used in the United States (the dose-response in rats, however, is clearly sublinear) (*45*). The possible hazard of diethylstilbestrol residues in meat from treated farm animals seems miniscule relative to endogenous estrogenic hormones and plant estrogens (*46*). Some natural carcinogens are also widely used as additives, such as allyl isothiocyanate (*47*), estragole (*48*), and alcohol (*23*).

Air pollution. A person inhales about 20,000 liters of air in a day; thus, even modest contamination of the atmosphere can result in inhalation of appreciable doses of a pollutant. This can be seen in the possible hazard in mobile homes from formaldehyde (HERP = 2.1%) or in conventional homes from formaldehyde (HERP = 0.6%) or benzene (HERP = 0.004%; Table 1). Indoor air pollution is, in general, worse than outdoor air pollution, partly because of cigarette smoke. The most important indoor air pollutant may be radon gas. Radon is a natural radioactive gas that is present in the soil, gets trapped in houses, and gives rise to radioactive decay products that are known to be carcinogenic for humans (*49*). It has been estimated that in 1 million homes in the United States the level of exposure to products of radon decay may be higher than that received by today's uranium miners. Two particularly contaminated houses were found that had a risk estimated to be equivalent to receiving about 1200 chest x-rays a day (49). Approximately 10% of the lung cancer in the United States has been tentatively attributed to radon pollution in houses (49). Many of these cancers might be preventable since the most hazardous houses can be identified and modified to minimize radon contamination.

General outdoor air pollution appears to be a small risk relative to the pollution inhaled by a smoker: one must breathe Los Angeles smog for a year to inhale the same amount of burnt material that a smoker (two packs) inhales in a day (12), though air pollution is inhaled starting from birth. It is difficult to determine cancer risk from outdoor air pollution since epidemiologists must accurately control for smoking and radon.

Some common drugs shown in Table 1 give fairly high HERP percentages, primarily because the dose ingested is high. However, since most medicinal drugs are used for only short periods while the HERP index is a daily dose rate for a lifetime, the possible hazard would usually be markedly less. We emphasize this in Table 1 by bracketing the numbers for these shorter exposures. Phenobarbital (HERP = 16%) was investigated thoroughly in humans who had taken it for decades, and there was no convincing evidence that it caused cancer (50). There is evidence of increased renal cancer in long-term human ingestion of phenacetin, an analgesic (51). Acetaminophen, a metabolite of phenacetin, is one of the most widely used over-the-counter pain killers. Clofibrate (HERP = 17%) is used as a hypolipidemic agent and is thought to be carcinogenic in rodents because it induces hydrogen peroxide production through peroxisome proliferation (52).

Occupational exposure can be remarkably high, particularly for volatile carcinogens, because about 10,000 liters of air are inhaled in a working day. For formaldehyde, the exposure to an average worker (HERP = 5.8%) is higher than most dietary intakes. For a number of volatile industrial carcinogens, the ratio of the permitted exposure limit [U.S. Occupational Safety and Health Administration (OSHA)] in milligrams per kilogram to the TD_{50} has been calculated; several are close to the TD_{50} in rodents and about two-thirds have permitted HERP values >1% (53). The possible hazard estimated for the actual exposure levels of the most heavily exposed EDB workers is remarkably high, HERP = 140% (Table 1). Though the dose may have been somewhat overestimated (54), it was still comparable to the dose causing cancer in half the rodents. An epidemiologic study of these heavily exposed EDB workers who inhaled EDB for over a decade did not show any increase in cancer, though because of the limited duration of exposure and the relatively small numbers of people monitored the study would not have detected a small effect (54, 55). OSHA still permits exposures above the TD_{50} level. California, however, lowered the permitted level over 100-fold in 1981. In contrast with these heavy workplace exposures, the Environmental Protection Agency (EPA) has banned the use of EDB for fumigation because of the residue levels found in grain (HERP = 0.0004%).

Uncertainties in Relying on Animal Cancer Tests for Human Prediction

Species variation. Though we list a possible hazard if a chemical is a carcinogen in a rat but not in a mouse (or vice versa), this lack of agreement raises the possibility that the risk to humans is nonexistent. Of 392 chemicals in our database tested in both rats and mice, 226 were carcinogens in at least one test, but 96 of these were positive in the mouse and negative in the rat or vice versa (56). This discordance occurs despite the fact that rats and mice are very closely related and have short life-spans. Qualitative extrapolation of cancer risks from rats or mice to humans, a very dissimilar long-lived species, is unlikely to be as reliable. Conversely, important human carcinogens may not be detected in standard tests in rodents; this was true for a long time for both tobacco smoke and alcohol, the two largest identified causes of neoplastic death in the United States.

For many of the chemicals considered rodent carcinogens, there may be negative as well as positive tests. It is difficult to deal with negative results satisfactorily for several reasons, including the fact that some chemicals are tested only once or twice, while others are tested many times. The HERP index ignores negative tests. Where there is species variation in potency, use of the more sensitive species, as is generally done and as is done here, could introduce a tendency to overestimate possible hazards; however, for most chemicals that are positive in both species, the potency is similar in rats and mice (57). The HERP may provide a rough correlate of human hazard from chemical exposure; however, for a given chemical, to the extent that the potency in humans differs from the potency in rodents, the relative hazard would be different.

Quantitative uncertainties. Quantitative extrapolation from rodents to humans, particularly at low doses, is guesswork that we have no way of validating (1, 5, 10, 11, 58). It is guesswork because of lack of knowledge in at least six major areas: (i) the basic mechanisms of carcinogenicity; (ii) the relation of cancer, aging, and life-span (1, 10, 42, 59); (iii) the timing and order of the steps in the carcinogenic process that are being accelerated; (iv) species differences in metabolism and pharmacokinetics; (v) species differences in anticarcinogens and other defenses (1, 60); and (vi) human heterogeneity—for example, pigmentation affects susceptibility to skin cancer from ultraviolet light. These sources of uncertainty are so numerous, and so substantial, that only empirical data will resolve them, and little of this is available.

Uncertainties due to mechanism in multistage carcinogenesis. Several steps (stages) are involved in chemical carcinogenesis, and the dose-response curve for a carcinogen might depend on the particular stage(s) it accelerates (58), with multiplicative effects if several stages are affected. This multiplicative effect is consistent with the observation in human cancer that synergistic effects are common. The three steps of carcinogenesis that have been analyzed in most detail are initiation (mutation), promotion, and progression, and we discuss these as an aid to understanding aspects of the dose-response relation.

Mutation (or DNA damage) as one stage of the carcinogenic process is supported by various lines of evidence: association of active forms of carcinogens with mutagens (61), the changes in DNA sequence of oncogenes (62), genetic predisposition to cancer in human diseases such as retinoblastoma (63) or DNA-repair deficiency diseases such as xeroderma pigmentosum (64). The idea that genotoxic carcinogens might show a linear dose-response might be plausible if only the mutation step of carcinogenesis was accelerated and if the induction of repair and defense enzymes were not significant factors (65).

Promotion, another step in carcinogenesis, appears to involve cell proliferation, or perhaps particular types of cell proliferation (66), and dose-response relations with apparent thresholds, as indicated by various lines of evidence: (i) The work of Trosko *et al.* (67) on promotion of carcinogenesis due to interference with cell-cell communication, causing cell proliferation. (ii) Rajewsky's and other work indicating initiation by some carcinogenic agents appears to require proliferating target cells (68). (iii) The work of Farber *et al.* (69) on liver carcinogenesis supports the idea that cell proliferation (caused by partial hepatectomy or cell killing) can be an important aspect of hepatocarcinogenesis. They have also shown for several chemicals that hepatic cell killing shows a toxic threshold with dose. (iv) Work on carcinogenesis in the pancreas, bladder and stomach

(*70*), and other tissues (*58*) is also consistent with results on the liver (*71, 72*) though the effect of cell proliferation might be different in tissues that normally proliferate. (v) The work of Mirsalis *et al.* (*71*) suggests that a variety of nongenotoxic agents are hepatocarcinogens in the B6C3F1 mouse (commonly used in cancer tests) because of their toxicity. Other studies on chloroform and trichloroethylene also support this interpretation (*72, 73*). Cell proliferation resulting from the cell killing in the mouse liver shows a threshold with dose (*71*). Also relevant is the extraordinarily high spontaneous rates of liver tumors (21% carcinomas, 10% adenomas) in the male B6C3F1 mouse (*74*). These spontaneous tumors have a mutant *ras* oncogene, and thus the livers in these mice appear to be highly initiated (mutated) to start with (*75*). (vi) Oncogenes: As Weinberg (*62*) has pointed out, "Oncogene-bearing cells surrounded by normal neighbors do not grow into a large mass if they carry only a single oncogene. But if the normal neighbors are removed . . . by killing them with a cytotoxic drug . . . then a single oncogene often suffices." (vii) Cell killing, as well as mutation, appears to be an important aspect of radiation carcinogenesis (*76*).

Promotion has also been linked to the production of oxygen radicals, such as from phagocytic cells (*77*). Since chronic cell killing would usually involve inflammatory reactions caused by neutrophils, one would commonly expect chemicals tested at the maximally tolerated dose (MTD) to be promoters because of the chronic inflammation.

Progression, another step in carcinogenesis, leading to selection for invasiveness and metastases, is not well understood but can be accelerated by oxygen radicals (*78*).

Chronic cell toxicity caused by dosing at the MTD in rodent cancer bioassays thus not only could cause inflammation and cell proliferation, but also should be somewhat mutagenic and clastogenic to neighboring cells because of the release of oxygen radicals from phagocytosis (*12, 79, 80*). The respiratory burst from phagocytic neutrophils releases the same oxidative mutagens produced by radiation (*77, 79*). Thus, animal cancer tests done at the MTD of a chemical might commonly stimulate all three steps in carcinogenesis and be positive because the chemical caused chronic cell killing and inflammation with some mutagenesis. Some of the considerable human evidence for chronic inflammation contributing to carcinogenesis and also some evidence for and against a general effect of inflammation and cytotoxicity in rodent carcinogenesis have been discussed (*81*).

Another set of observations may also bear on the question of toxicity and extrapolation. Wilson, Crouch, and Zeise (*82*) have pointed out that among carcinogens one can predict the potency in high-dose animal cancer experiments from the toxicity (the LD_{50}) of the chemical, though one cannot predict whether the substance is a carcinogen. We have shown that carcinogenic potency values are bounded by the MTD (*57*). The evidence from our database suggests that the relationship between TD_{50} and MTD has a biological as well as a statistical basis (*57*). We postulate that a just sublethal level of a carcinogen causes cell death, which allows neighboring cells to proliferate, and also causes oxygen radical production from phagocytosis and thus chronic inflammation, both important aspects of the carcinogenic process (*57*). The generality of this relationship and its basis needs further study.

If most animal cancer tests done at the MTD are partially measuring cell killing and consequent cell proliferation and phago-ic oxygen radical damage as steps in the carcinogenic process, one predict that the dose-response curves would generally be nonlinear. For those experiments in our database for which life table data (*14*) were available, a detailed analysis (*83*) shows that the dose-response relationships are more often consistent with a quadratic (or cubic) model than with a linear model.

Experimentally, it is very difficult to discriminate between the various extrapolation models at low doses (*11, 56*). However, evidence to support the idea that a nonlinear dose-response relationship is the norm is accumulating for many nongenotoxic and some genotoxic carcinogens. Dose-response curves for saccharin (*45*), butylated hydroxyanisole [BHA (*84*)], and a variety of other nongenotoxic carcinogens appear to be nonlinear (*85*). Formaldehyde, a genotoxic carcinogen, also has a nonlinear dose response (*28, 29*). The data for both bladder and liver tumors in the large-scale study on acetylaminofluorene, a genotoxic chemical, could fit a hockey stick–shaped curve, though a linear model, with a decreased effect at lower dose rates when the total dose is kept constant (*86*), has not been ruled out.

Carcinogens effective at both mutating and killing cells (which includes most mutagens) could be "complete" carcinogens and therefore possibly more worrisome at doses far below the MTD than carcinogens acting mainly by causing cell killing or proliferation (*15*). Thus, all carcinogens are not likely to be directly comparable, and a dose of 1/100 the TD_{50} (HERP = 1%) might be much more of a carcinogenic hazard for the genotoxic carcinogens dimethylnitrosamine or aflatoxin than for the apparently nongenotoxic carcinogens trichloroethylene, PCBs, or alcohol (HERP values marked with asterisks in Table 1). Short-term tests for mutagenicity (*41, 87*) can have a role to play, not only in understanding mechanisms, but also in getting a more realistic view of the background levels of potential genotoxic carcinogens in the world. Knowledge of mechanism of action and comparative metabolism in rodents and humans might help when estimating the relative importance of various low-dose exposures.

Human cancer, except in some occupational or medicinal drug exposures, is not from high (just subtoxic) exposures to a single chemical but is rather from several risk factors often combined with a lack of antirisk factors (*60*); for example, aflatoxin (a potent mutagen) combined with an agent causing cell proliferation, such as hepatitis B virus (*19*). High salt [a possible risk factor in stomach cancer (*13*)] and high fat [a possible risk factor in colon cancer (*4*)] both appear to be effective in causing cell killing and cell proliferation.

Risk from carcinogenesis is not linear with time. For example, among regular cigarette smokers the excess annual lung cancer incidence is approximately proportional to the fourth power of the duration of smoking (*88*). Thus, if human exposures in Table 1 are much shorter than the lifetime exposure, the possible hazard may be markedly less than linearly proportional.

A key question about animal cancer tests and regulatory policy is the percentage of tested chemicals that will prove to be carcinogens (*89*). Among the 392 chemicals in our database that were tested in both rats and mice, 58% are positive in at least one species (*14*). For the 64 "natural" substances in the group, the proportion of positive results is similar (48%) to the proportion of positive results in the synthetic group (60%). One explanation offered for the high proportion of positive results is that more suspicious chemicals are being tested (for example, relatives of known carcinogens), but we do not know if the percentage of positives would be low among less suspicious chemicals. If toxicity is important in carcinogenicity, as we have argued, then at the MTD a high percentage of all chemicals might be classified as "carcinogens."

The Background of Natural Carcinogens

The object of this article is not to do risk assessment on naturally occurring carcinogens or to worry people unduly about an occasional raw mushroom or beer, but to put the possible hazard of man-made carcinogens in proper perspective and to point out that we lack the knowledge to do low-dose "risk assessment." We also are almost completely ignorant of the carcinogenic potential of the enormous background of natural chemicals in the world. For example, cholinesterase inhibitors are a common class of pesticides, both man-made and natural. Solanine and chaconine (the main alkaloids in potatoes) are cholinesterase inhibitors and were introduced generally into the human diet about 400 years ago with the dissemination of the potato from the Andes. They can be detected in the blood of almost all people (*12, 90*). Total alkaloids are present at a level of 15,000 μg per 200-g potato with not a large safety factor (about sixfold) from the toxic level for humans (*91*). Neither alkaloid has been tested for carcinogenicity. By contrast, malathion, the main synthetic organophosphate cholinesterase inhibitor in our diet (17 μg/day) (*16*), is not a carcinogen in rodents.

The idea that nature is benign and that evolution has allowed us to cope perfectly with the toxic chemicals in the natural world is not compelling for several reasons: (i) there is no reason to think that natural selection should eliminate the hazard of carcinogenicity of a plant toxin that causes cancer in old age past the reproductive age, though there could be selection for resistance to the acute effects of particular carcinogens. For example, aflatoxin, a mold toxin that presumably arose early in evolution, causes cancer in trout, rats, mice, and monkeys, and probably people, though the species are not equally sensitive. Many of the common metal salts are carcinogens (such as lead, cadmium, beryllium, nickel, chromium, selenium, and arsenic) despite their presence during all of evolution. (ii) Given the enormous variety of plant toxins, most of our defenses may be general defenses against acute effects, such as shedding the surface lining of cells of our digestive and respiratory systems every day, protecting these surfaces with a mucin layer, having detoxifying enzymes that are often inducible, such as cytochrome P-450, conjugating enzymes, and glutathione transferases; and having DNA repair enzymes, which would be useful against a wide variety of ingested toxic chemicals, both natural and synthetic. Some human cancer may be caused by interfering with these normal protective systems. (iii) The human diet has changed drastically in the last few thousand years, and most of us are eating plants (such as coffee, potatoes, tomatoes, and kiwi fruit) that our ancestors did not. (iv) Normal metabolism produces radiomimetic mutagens and carcinogens, such as hydrogen peroxide and other reactive forms of oxygen. Though we have defenses against these agents, they still may be major contributors to aging and cancer. A wide variety of external agents may disturb this balance between damage and defense (*12, 42*).

Implications for Decision-Making

For all of these considerations, our scale is not a scale of risks to humans but is only a way of setting priorities for concern, which should also take into account the numbers of people exposed. It should be emphasized that it is a linear scale and thus may overestimate low potential hazards if, as we argue above, linearity is not the normal case, or if nongenotoxic carcinogens are not of very much concern at doses much below the toxic dose.

Thus, it is not scientifically credible to use the results from rodent tests done at the MTD to directly estimate human risks at low doses. For example, an EPA "risk assessment" (*92*) based on a succession of worst case assumptions (several of which are unique to EDB) concluded that EDB residues in grain (HERP = 0.0004%) could cause 3 cases of cancer in 1000 people (about 1% of all U.S. cancer). A consequence was the banning of the main fumigant in the country. It would be more reasonable to compare the possible hazard of EDB residues to that of other common possible hazards. For example, the aflatoxin in the average peanut butter sandwich, or a raw mushroom, are 75 and 200 times, respectively, the possible hazard of EDB. Before banning EDB, a useful substance with rather low residue levels, it might be reasonable to consider whether the hazards of the alternatives, such as food irradiation, or the consequences of banning, such as increased mold contamination of grain, pose less risk to society. Also, there is a disparity between OSHA not regulating worker exposures at a HERP of 140%, while the EPA bans the substance at a HERP of 0.0004%. In addition, the FDA allows a possible hazard up to a HERP of 0.3% for peanut butter (20 ppb), and there is no warning about buying comfrey pills.

Because of the large background of low-level carcinogenic and other (*93*) hazards, and the high costs of regulation, priority setting is a critical first step. It is important not to divert society's attention away from the few really serious hazards, such as tobacco or saturated fat (for heart disease), by the pursuit of hundreds of minor or nonexistent hazards. Our knowledge is also more certain about the enormous toll of tobacco—about 350,000 deaths per year (*1, 2*).

There are many trade-offs to be made in all technologies. Trichloroethylene and tetrachloroethylene (perchloroethylene) replaced hazardous flammable solvents. Modern synthetic pesticides displaced lead arsenate, which was a major pesticide before the modern chemical era. Lead and arsenic are both natural carcinogens. There is also a choice to be made between using synthetic pesticides and raising the level of plants' natural toxins by breeding. It is not clear that the latter approach, even where feasible, is preferable. For example, plant breeders produced an insect-resistant potato, which had to be withdrawn from the market because of its acute toxicity to humans due to a high level of the natural plant toxins solanine and chaconine (*12*).

This analysis on the levels of synthetic pollutants in drinking water and of synthetic pesticide residues in foods suggests that this pollution is likely to be a minimal carcinogenic hazard relative to the background of natural carcinogens. This result is consistent with the epidemiologic evidence (*1*). Obviously prudence is desirable with regard to pollution, but we do need to work out some balance between chemophobia with its high costs to the national wealth, and sensible management of industrial chemicals (*94*).

Human life expectancy continues to lengthen in industrial countries, and the longest life expectancy in the world is in Japan, an extremely crowded and industrialized country. U.S. cancer death rates, except for lung cancer due to tobacco and melanoma due to ultraviolet light, are not on the whole increasing and have mostly been steady for 50 years. New progress in cancer research, molecular biology, epidemiology, and biochemical epidemiology (*95*) will probably continue to increase the understanding necessary for lengthening life-span and decreasing cancer death rates.

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48. Estragole, one of [illegible] compounds in plants, is present in the [illegible] of many edible plants, including basil, [illegible], bay, anise, and fennel, as well as in [illegible] and vegetables [A. Y. Leung, *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics* (Wiley, New York, 1980)]. Dried basil has a volatile oil content of from 1.5 to 1.6%, which contains (on average) 70% estragole [H. B. Heath, *Source Book of Flavors* (AVI, Westport, CT, 1981), pp. 222–223]. Estragole is used commercially in [illegible]. It is added to beverages, candy, baked goods, [illegible], and condiments at average levels ranging from 2 to 100 ppm [NAS/NRC Food Protection Committee, Food and Nutrition Board, *Chemicals Used in Food Processing* (NAS/NRC Publ. No. 1274, National Academy of Sciences, Washington, DC, 1965), p. 116].
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96. A national survey of U.S. drinking water supplies identified the concentrations of about 20 organic compounds. The mean total trihalomethane concentration was 117 μg/liter, with the major component, chloroform, present at a mean concentration of 83 μg/liter (83 ppb). Raw water that is relatively free of organic matter results in drinking water relatively free of trihalomethanes after chlorination. These studies are reviewed in S. J. Williamson, *The Science of the Total Environment* 18, 187 (1981).
97. Public and private drinking water wells in Santa Clara Valley, California, have been found to be contaminated with a variety of halogenated hydrocarbons in small amounts. Among 19 public water system wells, the most commonly found contaminants were 1,1,1-trichloroethane (TCA), and 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113). TCA was found in 10 wells generally at concentrations of less than 30 ppb, though one well contained up to 8800 ppb, and Freon 113 was found in six wells at concentrations up to 12 ppb. [illegible] higher because the water is not mixed with water from other sources [California Department of Health Services, California Regional Water Quality Control Board 2, Santa Clara County Public Health Department, Santa Clara Valley Water District, U.S. Environmental Protection Agency, *Ground Water and Drinking Water in the Santa Clara Valley: A White Paper* (1984), table 8]. Trichloroethylene may not be a carcinogen in humans at low doses [R. D. Kimbrough, F. L. Mitchell, V. N. Houk, *J. Toxicol. Environ. Health* 15, 369 (1985)].
98. Contaminated drinking water in the town of Woburn, Massachusetts, was found to contain 267 ppb trichloroethylene, 21 ppb tetrachloroethylene, 12 ppb chloroform, 22 ppb 1,2-*trans*-dichloroethylene, and 28 ppb 1,2-*cis*-dichloroethylene [S. W. Lagakos, B. J. Wessen, M. Zelen, *J. Am. Stat. Assoc.* 81, 583 (1986)].
99. The amount of chloroform absorbed by a 6-year-old child in a chlorinated freshwater swimming pool has been estimated [J. A. Beech, *Med. Hypotheses* 6, 303 (1980), Table 1] [illegible] U. Lahl, J. Vondberg, B. Gabel, B. Stachel, W. Thiemann [*Water Res.* 15, 803 (1981)] [illegible].
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101. The average adult daily PCB intake from food estimated by the FDA in fiscal years 1981/1982 was 0.2 μg/day (26). Many slightly different PCB mixtures have been studied in long-term animal cancer bioassays; the calculation of TD_{50} was from a test of Aroclor 1260 which was more potent than other PCBs (34).
102. The average consumption of EDB residues in grains has been estimated by the EPA for adults as 0.420 μg kg^{-1} day^{-1} and for children as 0.013 μg kg^{-1} day^{-1} [U.S. EPA Office of Pesticide Programs, *Ethylene Dibromide (EDB) Scientific Support and Decision Document for Grain and Grain Milling Fumigation Uses* (8 February 1984)].
103. The leaves and roots of Russian comfrey are widely sold in health food stores and are consumed as a medicinal herb or salad plant or are brewed as a tea. Comfrey leaf has been shown to contain 0.01 to 0.15%, by weight, total pyrrolizidine alkaloids, with an average level of 0.05% for intermediate size leaves [C. C. J. Culvenor, J. A. Edgar, J. L. Frahn, L. W. Smith, *Aust. J. Chem.* 33, 1105 (1980)]. The main pyrrolizidine alkaloids present in comfrey leaves are echimidine and 7-acetylintermedine, neither of which has been tested for carcinogenicity. Almost all tested 1,2-unsaturated pyrrolizidine alkaloids have been shown to be genotoxic and carcinogenic [H. Mori *et al.*, *Cancer Res.* 45, 3125 (1985)]. Symphytine accounts for [illegible] of the total alkaloid in the leaves and has been shown to be carcinogenic [C. C. J. Culvenor *et al.*, *Experientia* 36, 377 (1980)]. We assume that 1.5 g of intermediate size leaves are used per cup of comfrey tea (Table 1). The primary alkaloids in comfrey roots are [illegible] (0.47 g per kilogram of root) and [illegible] (0.3 g per kilogram of root) [T. Furuya and M. Hikichi, *Phytochemistry* 10, 2217 (1971)]. Comfrey-pepsin tablets (300 mg of root per tablet) have a recommended dose of one to three tablets three times per day. Comfrey roots and leaves both induce liver tumors in rats [I. Hirono, H. Mori, M. Haga, *J. Natl. Cancer Inst.* 61, 865 (1978)], and the TD_{50} value is based on these results. Three pyrrolizidine alkaloids tested have been found to be at least

as potent as carcinogens such as symphytine. If the other pyrrolizidine alkaloids in comfrey were as potent carcinogens as symphytine, the possible hazard of a daily cup of tea would be HERP = 0.6% and that of a daily root tablet would be HERP = 7.3%.

104. *Agaricus bisporus* is the most commonly eaten mushroom in the United States with an estimated annual consumption of 340 million kilograms in 1984–85. Mushrooms contain various hydrazine compounds, some of which have been shown to cause cancer in mice. Raw mushrooms fed over a lifetime to male and female mice induced bone, forestomach, liver, and lung tumors [B. Toth and J. Erickson, *Cancer Res.* 46, 4007 (1986)]. The 15-g raw mushroom is given as wet weight. The TD_{50} value based on the above report is expressed as dry weight of mushrooms so as to be comparable to other values for TD_{50} in Table 1; 90% of a mushroom is assumed to be water. A second mushroom, *Gyromitra esculenta*, has been similarly studied and found to contain a mixture of carcinogenic hydrazines [B. Toth, *J. Environ. Sci. Health* C2, 51 (1984)]. These mushrooms are eaten in considerable quantities in several countries, though less frequently in the United States.

105. Safrole is the main component (up to 90%) of oil of sassafras, formerly used as the main flavor ingredient in root beer [J. B. Wilson, *J. Assoc. Off. Anal. Chem.* 42, 696 (1959); A. Y. Leung, *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics* (Wiley, New York, 1980)]. In 1960, safrole and safrole-containing sassafras oils were banned from use in foods in the United States [*Fed. Regist.* 25, 12412 (1960)]. Safrole is also naturally present in the oils of sweet basil, cinnamon leaf, nutmeg, and pepper.

106. Diet cola available in a local market contains 7.9 mg of sodium saccharin per fluid ounce.

107. Metronidazole is considered to be the drug of choice for trichomonal and *Gardnerella* infections [AMA Division of Drugs, *AMA Drug Evaluations* (American Medical Association, Chicago, IL, ed. 5, 1983), pp. 1717 and 1800].

108. Isoniazid is used both prophylactically and as a treatment for active tuberculosis. The adult prophylactic dose (300 mg daily) is continued for 1 year [AMA Division of Drugs, *AMA Drug Evaluations* (American Medical Association, Chicago, IL, ed. 5, 1983), pp. 1766–1777].

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Perception of Risk

PAUL SLOVIC

Studies of risk perception examine the judgments people make when they are asked to characterize and evaluate hazardous activities and technologies. This research aims [illegible]id risk analysis and policy-making by (i) providing a [illegible] for understanding and anticipating public responses [illegible]azards and (ii) improving the communication of risk information among lay people, technical experts, and decision-makers. This work assumes that those who promote and regulate health and safety need to understand how people think about and respond to risk. Without such understanding, well-intended policies may be ineffective.

THE ABILITY TO SENSE AND AVOID HARMFUL ENVIRONMENTAL conditions is necessary for the survival of all living organisms. Survival is also aided by an ability to codify and learn from past experience. Humans have an additional capability that allows them to alter their environment as well as respond to it. This capacity both creates and reduces risk.

In recent decades, the profound development of chemical and nuclear technologies has been accompanied by the potential to cause catastrophic and long-lasting damage to the earth and the life forms that inhabit it. The mechanisms underlying these complex technologies are unfamiliar and incomprehensible to most citizens. Their most harmful consequences are rare and often delayed, hence difficult to assess by statistical analysis and not well suited to management by trial-and-error learning. The elusive and hard to manage qualities of today's hazards have forced the creation of a new [illegible]ual discipline called risk assessment, designed to aid in [illegible]ng, characterizing, and quantifying risk (*1*).

[illegible]reas technologically sophisticated analysts employ risk assessment to evaluate hazards, the majority of citizens rely on intuitive risk judgments, typically called "risk perceptions." For these people, experience with hazards tends to come from the news media, which rather thoroughly document mishaps and threats occurring throughout the world. The dominant perception for most Americans (and one that contrasts sharply with the views of professional risk assessors) is that they face more risk today than in the past and that future risks will be even greater than today's (*2*). Similar views appear to be held by citizens of many other industrialized nations. These perceptions and the opposition to technology that accompanies them have puzzled and frustrated industrialists and regulators and have led numerous observers to argue that the American public's apparent pursuit of a "zero-risk society" threatens the nation's political and economic stability. Wildavsky (*3*, p. 32) commented as follows on this state of affairs.

> How extraordinary! The richest, longest lived, best protected, most resourceful civilization, with the highest degree of insight into its own technology, is on its way to becoming the most frightened.
>
> Is it our environment or ourselves that have changed? Would people like us have had this sort of concern in the past? . . . Today, there are risks from numerous small dams far exceeding those from nuclear reactors. Why is the one feared and not the other? Is it just that we are used to the old or are some of us looking differently at essentially the same sorts of experience?

During the past decade, a small number of researchers has been attempting to answer such questions by examining the opinions that people express when they are asked, in a variety of ways, to evaluate hazardous activities, substances, and technologies. This research has attempted to develop techniques for assessing the complex and subtle opinions that people have about risk. With these techniques, researchers have sought to discover what people mean when they say that something is (or is not) "risky," and to determine what factors underlie those perceptions. The basic assumption underlying these efforts is that those who promote and regulate health and safety need to understand the ways in which people think about and respond to risk.

The author is president of Decision Research, 1201 Oak Street, Eugene, OR 97401, and professor of psychology at the University of Oregon.

Mr. KIMM. Senator, maybe it would help if I submit it for the record. I do not remember the pesticides at the top of that list, but I do remember in general the high risk pesticides were ones that we either had regulated or were in the process of re-reviewing. Perhaps if I submit for the record the status of the particular pesticides that you have identified, you will see that, in fact, what I am saying is true. As we set priorities to go back and look at old pesticides, we, in fact, dealt with them on a risk basis as we understood that risk. And so I suspect that a number of the pesticides that are at the top of that list are being reviewed now or have been reviewed and dealt with. I would be happy to supply that for the record.

Senator HARKIN. I would like to see it.

At a hearing on the Children, Family, Drugs and Alcoholism held March 16, I requested data on EPA's regulation of inert ingredients in pesticide products. I still have not received a response on that, and I hope you will look into getting a response to me.

The CHAIRMAN. Would the Senator yield just for a question in this area?

Senator HARKIN. Yes.

The CHAIRMAN. Mr. Kimm, did you make any recommendations to OMB on any of these items? Has your Department made any recommendations on pesticide regulation? Have you made any recommendations to OMB?

Mr. KIMM. No. I think the answer is no in terms of OMB is not the way these particular decisions get made. There is an OMB point in which they are often interested in what is being done, but this is a problem of working its way through the science, and the work that the Agency does in that regard is done with advisory committees and in a goldfish bowl. We can provide you with the status of any array of pesticides that you would like as we have been able to work them through.

The heart of the problem here has historically been resources to get after the old pesticides. In the amendments that passed Congress in 1988, you established the biggest fee system that I know anything about to fund an accelerated exercise at going back and cleaning up these old pesticides, forcing the generation of all the scientific data to update our assessment of risks and to make regulatory changes when appropriate, and we are into implementing that. And as I said earlier in my comments, I think that is where the risk reduction potential is greatest in this program.

Senator HARKIN. If I might, Mr. Chairman, I just want to put in the record here an article from the May 26, 1989 issue of the Des Moines Register.

[The article referred to follows:]

TOO MANY CHEMICALS USED IN FARMING, FARMERS SAY

BY VERONICA FOWLER

AMES, IA.—More than three out of every four Iowa farmers believe that modern farming relies too heavily on chemicals, a survey by Iowa State University indicates.

Seventy-six percent of the 2,007 Iowa farmers polled said they agree with the statement that modern farming relies too heavily upon chemical fertilizers. About the same percentage—78 percent—said they believe modern farming relies too much on insecticides and herbicides.

Paul Lasley, ISU extension sociologist, and Michael Duffy, extension economist, asked farmers their opinions on low-input farming methods as part of the 1989 Iowa Farm and Rural Life Poll, an annual poll conducted by Iowa State.

Lasley said the poll chose the topic of low-input agriculture—a practice that includes minimum usage of chemicals—"because of the public concern about the safety of some modern farming practices." It was the first time the poll covered the use of farm chemicals.

Sixty-nine percent of the farmers polled said they agreed that the increased use of low-input farming practices would help maintian natural resources. Nineteen percent were uncertain, and 12 percent disagreed.

However, nearly half the farmers polled—46 percent—said they agreed that the need for an adequate food supply limits the use of low-input farming in commercial operations. About one-fourth disagreed, and another fourth were uncertain.

A little more than half—56 percent—said they disagreed that there was too much concern about food safety issues, and 30 percent said they agreed that there was indeed too much concern.

Fifty-six percent said they agreed that farmers would use more low-input farming methods if more research information were available. Thirty-one percent were uncertain, and the rest disagreed.

Those farmers polled also were asked to rank sources of water pollution according to their severity.

Forty-two percent listed industrial wastes as the most severe, and 30 percent ranked run-off of pesticides and fertilizer as the most serious. Nineteen percent ranked leaching of pesticides and fertilizers as the most serious, while just 10 percent ranked soil erosion sediment as the most serious. Sewage from towns and cities was ranked as the most serious by 8 percent of the respondents; 3 percent ranked animal waste as the most serious. Some ranked more than one source as the most serious, putting the total at more than 100 percent.

The release of the poll came on the heels of an Iowa State University four-day conference on biotechnology and sustainable agriculture.

Lasley, however, said the release of the report was unrelated to that conference.

Lisa Drake, a spokesperson with Monsanto County in St. Louis, MO, said she believed it was hard for such a poll to get a reading on an issue as complex as low-input farming.

One problem, said Drake, is that the poll doesn't define low-input farming. Also, she said, it doesn't name specific chemicals, which can vary widely in safety.

Senator HARKIN. Iowa State University just did a poll of farmers in Iowa. These are farmers, active farmers, and more than three out of every four Iowa farmers believe that modern farming relies too heavily on chemicals. Seventy-six percent of the 2,007 Iowa farmers polled said they agree with the statement that modern farming relies too heavily upon chemical fertilizers. About the same percentage, 78 percent, said they believe modern farming relies too much on insecticides and herbicides. But then they said 56 percent said they agreed that farmers would use more low-input farming methods of more research information were available. Then over half of them, 56 percent, said that the reason they are doing it is because we need an adequate food supply at low cost. So I am just telling you what farmers are thinking.

I got to tell you, the number of cancers that are occurring on the farms in my State are alarming. Alarming. I had one square mile where there were five cancer deaths within a very short period of time, in one square mile, in one area of Iowa. My home town has 151 people. I cannot tell you how many people are dying of cancer, young people. I just met a farmer this weekend whose wife just passed away from cancer. She was less than 50 years old. I am telling you, these people are thinking about this.

I cannot say absolutely what is causing it, but I can tell you what they think. I can tell you what they think is causing it, and something has got to be done to—first of all, you get a food scare every month, and something has got to be done about that. Second, farmers are getting very upset about the tremendous use of chemicals that they are using because they see what is happening around them. Yet we cannot get any kind of reliable data, reliable information. We cannot get people to agree upon a risk assessment.

If the scientists cannot agree, I do not know where that leaves us.

Dr. YOUNG. Senator, if I could please add, because that reinforces Senator Hatch's question. I believe there is broad agreement in the scientific community that today an upper-bound risk number of negligible risk is one in a million. I do not think there is a substantial disagreement about that. As a physician and a person who has had cancer myself, I believe there is a great concern about cancer. There is a very interesting set of articles that I will give you as preliminary information that shows that one of the most significant issues that we have to deal with is caloric restriction. There are nice data to show a correlation with obesity and increased incidence of cancers and the inability of the animal to at least manage carcinogens taken in.

But your frustration and my frustration is the same. When we are at a cutting edge of science, it is incredibly confusing. And I believe that we owe, just as Senator Hatch emphasized, the Nation the best risk assessment that we can, and that we have got to do it in a unified fashion. On our scale—and I can provide you data—the reason that we focused on the safety issues that we did earlier in some of the pesticides is that we have got—and I have submitted for the record some analysis of what is in the food supply in relation to the daily allowable intake. Under those circumstances, we find that only 1.5 percent of the domestic pesticides are in violation—I am sorry, or even any violation at all, and essentially none of them exceed the daily allowable intake. But what you are focusing on is let us get the right daily allowable intake, and that is just what we need to do.

Senator HARKIN. And also find out about the inert ingredients. No one has been looking at those.

Dr. YOUNG. I think that is a logical approach, and I believe EPA is committed——

Mr. KIMM. We are committed and into it. If we have not replied to an earlier question, we will get started on it right away. But, no, we are into implementing the strategy that I outlined earlier and, in fact, have seen several hundred product formulations changed to eliminate the inerts that we had identified earlier as the ones of toxicological concern. So that process is under way, Senator.

The CHAIRMAN. We have had a call at least for our side, for a meeting that we are going to have to leave for. I am going to have to leave by 11:30. I think the Senator from Iowa is as well. We still have another series of witnesses. I want to give the Senator from Mississippi a chance to ask questions, and then we will go to our next panel.

Senator COCHRAN. Thank you very much, Mr. Chairman.

One question comes to my mind; that is, as we seek to try to find a Federal standard and uniformity of enforcement rules and the like at the Federal level, what happens if we run into competition from State governments who decide they know better than the Federal Government how to deal with these issues? I do not know whether the bill the distinguished chairman has introduced attempts to deal with that——

The CHAIRMAN. It does not preempt.

Senator COCHRAN [continuing]. —but the real problem, as I see it is if we——

The CHAIRMAN. I am a States-righter on this issue. [Laughter.]

Senator COCHRAN. If we are going to do a better job and try to create a sense of confidence on the part of the consuming public in what the Federal Government says about these things, should we not try to address that issue? And if we do try to address it, how do we do it?

I have the image of someone coming into the supermarket, for example, and going to the produce area and seeing "USDA says this is okay," or just a stamp, "USDA OK." And then over in the next bin there is "State of Blank says this is safe." And then another says, "This other is very safe." And the consumer tends to be confused as to whether "very safe" is better than "OK USDA." How do we deal with that, and how does the person who is in the business of selling those goods deal with that, or the producers who are trying to get into the market deal with that?

Dr. YOUNG. Let me try, if I can, Mr. Cochran. I had the opportunity of chairing one of the committees on this for the Administration in the previous Administration. I hope these comments are appropriate.

I believe that health knows no State boundary, and an overlapping patchwork of rules on what is safe would lead to utter and mass confusion. If something is unsafe in Mississippi, it should be unsafe over the entire Nation. Therefore, I would support strongly not using that nasty word "pre-emption" but support strongly a uniform approach to safety where we look at—just as Senator Harkin said, if there is a list of chemicals for which concerns are raised by the Academy, then we tackle it as a Federal Government and once and for all decide whether these compounds pose no negligible risk or whether they pose a risk.

I held a meeting with both Agriculture and EPA, and the people from the consumer groups said: The most important thing that we want to know is whether it is safe or not safe. I think those are the two buckets. If it is safe, it is safe over the land. If it is not safe, it is unsafe over the land, and it should be removed. And under those circumstances, one embarks on a national program of uniformity to examine chemicals in compounds that are of potential health risks and does just what this bill does: establish a negligible risk standard. I think that is the right way to go.

Senator COCHRAN. My next question is this, then: In dealing with the realities that we have seen recently, the consuming public has a lack of confidence in terms of the warnings or the certification of safety or the nutritional value of foods. They do not really know who to believe, and that is a fact. We have hearings here in the Congress, and we have a celebrity person who may describe his concerns or her concerns about a matter, and that ends up being believed much more readily than a statement from the Food and Drug Administration or the Department of Agriculture or the Environmental Protection Agency. It is kind of an interesting situation that we are confronting here.

I wonder whether or not to try to build a bridge of confidence between the Federal Government's role in this area and the general public we should consider establishing a new super-agency on food safety and bring together the resources of the Department of Agriculture, the Food and Drug Administration, and EPA, whoever else, and have a one-stop, the-buck-stops-here agency on food safety. I am not threatening anybody with any kind of impulsive action on appropriations bills or in any other fashion. But I am just suggesting.

Now, here we are confronted with the reality of FDA having the responsibility to certify drugs, medical devices, a wide range of things, do inspections of imported foods. Remember the grapes from Chile.

Dr. YOUNG. I remember.

Senator COCHRAN. You are having to make decisions on things like this, and at the same time be the lead agency to certify whether or not foods are safe and nutritious as advertised. Your budget is so small in comparison with that responsibility, the numbers of people that you can really assign to these responsibilities. It is a very big problem. I know there is legislation to bolster the Food and Drug Administration and enlarge its authority in terms of funding and that kind of thing. I do not know whether that will do the job, though.

We have the Food Safety and Inspection Service in the Department of Agriculture, and as Secretary Parnell pointed out, their responsibility is limited pretty much to meat and poultry inspection. I think it should be enlarged, or somebody should start inspecting seafood. Do you know seafood is not inspected? There is legislation being drafted, and I am a part of a group trying to deal with that problem with a new bill. And I think we are going to make some progress and get that addressed.

I wonder what your reaction would be to that. I am not saying I am sold on it, but I wonder about it—a super-agency on food safety if I have wandered too far from my first suggestion.

Dr. YOUNG. Let me give it a try and then pass off to others. I think that you have raised a most important issue, but I have learned in the five years that I have been in Government, and earlier in the academic realm, that just reorganization does not address an issue. I like personally the concept of each agency focusing on its particular expertise. Going back to the tradition of our Government, we were founded on a balance of powers, if you will, so that we had checks and balances.

In a sense, we have checks and balances in this way. We have a Department of Agriculture that is promoting agricultural products but does want them safe. We have an EPA that is looking at pesticides and dealing with soil contamination, water contamination, etc. We have got a Food and Drug Administration that deals with the health aspects, and its tradition is health in concert with NIH and CDC and other protection agencies.

I think the issue is to make them all work together. My proposal would be more for strengthening them individually as required and getting it in a harmonious fashion. You could play the argument out: Do we need a Congress, a President, and a judicial system? In that same way, why not have just one thing?

I think that balance of power and the balance of responsibilities provides the best way. I do not think one-stop shopping would answer it. I would be opposed as a physician to leave out health and have it work on other areas. I come from the old standard that doctors, nurses, and others are important in taking care of your body and well-being. I usually go to a doctor when sick. I do not go to a coal miner—not that coal miners are not wise and respected, but I would not try to dig coal, and I am sure a coal miner would not try to prescribe medicines. And I think that that balance of dealing with promotion of food, safety of food, safety of the environment provides, a very sound balance of powers.

Senator Hatch and Senator Kennedy are correct. We have got to get our act together, and I think that is an important part of that ingredient.

Senator COCHRAN. Mr. Kimm, what is your reaction?

Mr. KIMM. I agree very much with what the commissioner has just said. As a practical matter, I do not think you get one-stop shopping anyway. For example, in pesticides, if there were a food agency, dietary impacts are only one of the concerns that we presently have in the health arena as it relates to pesticides. We have a great many concerns, for example, about groundwater contamination, and that gets you into a whole set of different questions about site-specific factors and vulnerability of settings and proximity to wells and that kind of thing. And so I do not think you could neatly take pesticides into a single agency and provide a one-stop shopping, if that is your goal.

I do share with the commissioner the view based on a lot of years in the Government that another big organization, if you do not deal with the fundamental issues, is not going to get you anywhere and is likely in the short run to create more confusion and slow everything down at a time when I think the American public is looking for us to speed things up, to get at looking at these old pesticides, to get at changing tolerances.

If I might, it seems to me the heart of the problem, though, that you have touched on, which I have spent a fair amount of time thinking about in view of recent events, is the quality of the public dialogue. I think we would all agree easily that an atmosphere of scare and distrust is not one in which we are likely to get any public understanding or participation in what it is that we are doing. And I think that we need to try to find ways of trying to get these complicated matters under scrutiny, debate, and what have you in a more thoughtful fashion.

Toward that end, it seems to me there are three realities that need to be accepted and debated and that will carry the public interest forward. One of them is we live in a very complicated society in which virtually nothing is risk free, totally risk free. That is our experience living in a complicated, industrial society. It is absolutely true of the use of chemicals in the production of food. There are some risks associated with everything. The question is: How much risk is reasonable or not reasonable?

In our society, we have assigned that responsibility to the Government, and depending on the legislation, we can get a lot of guidance on how to exercise that or it can be left to the discretion of the agency with people watching how the agency exercises that discretion. But I think that is the process. We need to demystify how it is that we regulate. We certainly are using the best science available. Our science is all on the conservative side. It tends to overestimate exposure. It tends to overestimate risk. We all know that, and we protect the very high levels of protection. That is what makes this system work. I do not think much of the American public really understands that, and yet it is impossible to kind of take that message in the heat of an ALAR or a media event of that kind of proportion.

Finally, it seems to me that there also needs to be a recognition that as we do our job, we go about getting more testing done, we are going to find more ALARs. There are going to be more pesticides which are going to show on more careful scrutiny bigger risks than we presently understand. And we need to get into a process in which we have a streamlined system for finding offensive pesticides and getting them off the market. And we have serious constraints in the framework that we operate under at the present time.

Senator COCHRAN. Mr. Parnell, your reaction to that?

Mr. PARNELL. Well, I share their views. I do not think a superagency will necessarily solve—having come from the State of California where the Department of Agriculture has the pesticide registration and enforcement within it. Certainly, we still have our share of problems, as you have alluded to indirectly earlier on. California has been very up front in a separate set of standards for the use of pesticides. I think little could be gained.

I think what should be encouraged—and I think Senator Hatch hit it right on the head—is to require a full cooperation between the agencies that are concerned and make sure that we are talking to each other in a regular way and have some agreement so that we do not feed the misimpressions or the misunderstandings that are going on. And, in fact, we could forcefully quell any misunderstanding that was out there. That certainly has not happened adequately in the past, is my experience, and I think we have talked recently and are dedicated to doing that.

The thing that is lost in all of these discussions—and I certainly have left the committee with the misimpression that we are divided. We are not divided. And it might be as a result of some inartful words put together. If I have done that, I apologize. What I mean to say and certainly think the point needs to be made here today is that most of the assumptions that have been made relative to food safety that have become public have been based on maximum allowable tolerance assumptions. They have been based on the fact that every pesticide registered for a use on a commodity was, in fact, used. They also are based on the fact that they were used according to the label; that is, maximum allowable strength. And we know from sampling our farmers throughout the country that, in fact, is not the case. In fact, only one pesticide—for example, on tomatoes—or two at the most may be used where there are six or seven registered. So that creates misunderstanding.

What I suggest when I say our food supply is safe is based on the monitoring currently going on not only by FDA but by the State of California who last year did 17,000 samples. That led to 1,248,000 analyses on 200 food crops, analyzing for every single pesticide that is used on a food crop. That analysis seems to suggest—and I think Dr. Young alluded to it earlier on—that we need to have a coordinated effort to make sure that every State that does this kind of work, together with FDA, should submit that data. He should be able to analyze that and make better interpretations of that data to give us some forceful statements as to whether or not he thinks, after analyzing that information, our food supply has any degree of risk attached to it.

USDA absolutely is currently dedicated to the utilization of less pesticides, trying to find alternative methods; in fact, LISA, or low-input sustainable agriculture, is something that we are spending money on. You have appropriated money for that purpose, and that, in fact, is ongoing. I think part of the misunderstanding comes out of not really being good at understanding all of the work that has been done out there, because the work that has been done seems to suggest that when you look at actual residues at the time of consumption, they are very, very small.

The CHAIRMAN. We have 20 minutes left.

Senator COCHRAN. Mr. Chairman, I appreciate your allocating me the time that you have. I would like to ask that my statement be made a part of the record.

The CHAIRMAN. It will be made a part of the record.

[The prepared opening statement of Senator Cochran follows:]

PREPARED OPENING STATEMENT OF SENATOR COCHRAN

Mr. Chairman:

I want to join you in welcoming our witnesses who will be discussing the issue of food safety. We are very fortunate to live in a country that has the safest food supply in the world. This has come about in part as a result of the very kind of activity that we are engaged in today ... continued efforts to improve the regulation process and to respond to the ever expanding scientific discoveries and methodologies which can have a direct impact on the safety of our food supply.

However, as we look at the particular legislation before us, S. 722, the Food Safety Amendments of 1989, we must be conscious of conflicts which may be created between the Federal Insecticide, Fungicide and Rodenticide Act and the Federal Food, Drug and Cosmetic Act, the two statutes under which pesticides are regulated. Also, we should address the conflicts among the states and the Federal Government in the development and enforcement of food safety standards.

Our goal is to make sensible improvements in the overall regulation of our food supply, not to create confusion in the food production and distribution system.

The CHAIRMAN. We will now hear from Dr. Benbrook, who is on the staff of the National Academy of Sciences and then we will make a determination whether we can hear the remaining witnesses or get them all back at another time to conclude the hearing. But I do want to give Dr. Benbrook at least the time that is available before we conclude.

I recognize the Senator from Utah.

Senator HATCH. If I could just make one other comment, Mr. Chairman. I need to point out to the public as a whole that we spend approximately half a million dollars—a little bit more than that—about $550 million on our meat inspection program in this country. The total FDA budget is less than that. The FDA is responsible for 25 percent of all of the products consumed in America. Now, that is amazing to me. So I have to apologize to you, too, because we have not done our job in seeing that FDA has what it needs to do its job.

Finally, finding alternatives to less safe products is a difficult thing because of "The Delaney Paradox."

Dr. YOUNG. Absolutely.

Senator HATCH. In 1983, I proposed legislation to reverse the Delaney clause so that all new products would be approved, or might be approved which possess a negligible risk of cancer. And we did that to replace those which have a higher risk. Under the present law this is not possible. I think Senator Harkin, showing that particular pesticides are grandfathered because of Delaney, makes a pretty good point. So this is a critical public health need, and we need the standards to be uniform or we are going to have, because of Proposition 65, 50 different standards in this country. And no manufacturer, no food supplier creator of consumer goods in this country can meet the standards in all 50 States. So we need a uniform standard, and I think if we did that, all Americans would have confidence in our food supply, and we would all be better off and we would all be safer.

Dr. YOUNG. I concur.

Senator HATCH. So I just wanted to make those comments, and I think all of you agree with that. You have got an important task to come back to us within the next two months and come up with a unified approach, and let us see if we can go from there.

The CHAIRMAN. Thank you very much.

Mr. KIMM. Thank you, Mr. Chairman.

The CHAIRMAN. We will permit the members of the committee to file written questions.

Mr. PARNELL. Thank you for having us.

The CHAIRMAN. We have Charles Benbrook, who is from the Board on Agriculture, National Academy of Sciences. I know there is an individual on the last panel, Gary Booth, who I am not sure we will be able to get to. He is from out of town. We also have David Roe who is from out of town. Why don't you both take a seat, and we can proceed. Then we will take the other two witnesses who are from Washington. We will try and proceed with them later, if that is all right, Senator Hatch.

Senator HATCH. I think that is great. I would just say this, that I am really pleased to have all of the witnesses here today, especially you three. Mr. Benbrook, you have done a terrific job in this area. David Roe, of course, has been the inspiration behind Proposition 65. And Gary Booth is a professor of zoology at the Brigham Young University out in Utah, an esteemed scientist in the area of food toxicology and a member of the BYU faculty. There are a lot of other things I would like to say about you, Gary, but in the interest of time, I will submit those for the record. We are just very proud to have you here.

Mr. BOOTH. Thank you.

The CHAIRMAN. If it is agreeable to the other members of the panel—I am very reluctant to do it, but we do have to leave. We will hear from each of them while we are here, and then, as I say, I am reluctant but have done it in the past, I might ask counsel both from the majority and minority to ask the questions of the different members.

Senator HATCH. That is agreeable.

The CHAIRMAN. We can file additional questions and I do think it is helpful to all of the members of our committee to hear all the witnesses. As I say, I am reluctant to do it, but we will hear from each.

STATEMENTS OF CHARLES BENBROOK, BOARD ON AGRICULTURE, NATIONAL ACADEMY OF SCIENCES, WASHINGTON, DC; DAVID ROE, SENIOR ATTORNEY, ENVIRONMENTAL DEFENSE FUND, OAKLAND, CA; AND GARY M. BOOTH, DIRECTOR, TOXICOLOGY RESEARCH LABORATORY AND PROFESSOR OF ZOOLOGY, BRIGHAM YOUNG UNIVERSITY, PROVO, UT

Mr. BENBROOK. Thank you, Mr. Chairman. I am delighted to have three minutes to explain a problem I have been studying for 8 years. [Laughter.]

The CHAIRMAN. No. You get five.

Mr. BENBROOK. First of all, Mr. Chairman, Senator Hatch, I would like to commend you for your past efforts to try to deal with this problem. It is a very complicated problem. Very few people understand the full implications of the legislation that has to be drafted to deal with the inconsistency between the Food, Drug and Cosmetic Act and FIFRA statute. The legislation, Mr. Chairman, that you have drafted with Congressman Waxman goes a very long way toward doing just that. It is long. Very few people understand it. There is much behind it, including this whole report of ours. In my statement, I go through a number of factors that need to be assessed in perfecting the impact of that legislation.

I would like to not spend the time addressing what is in the testimony and go directly to what I think are the two dominant political problems that the committee faces if you are going to be able to perfect and pass this legislation. First of all, the bill can be faulted because it is somewhat overly aggressive. You have been dealing with this problem for eight, ten years, this problem of public concern about pesticide residues in the diet, and recent events have brought public concern to such a fevered pitch that in crafting the current bill, it really has tried in a very short amount of time to wring virtually all the risk out of the food supply, not just from pesticide active ingredients but also from inert ingredients.

This fact has created a great deal of concern in the food industry and in the agricultural industry, concern that too many pesticides will be lost to production agriculture too fast. They are not sure if that is going to happen. No one really understands what the bill will do, but particularly the four-year and the six-year stand risk reduction goals in the bill are very difficult to estimate what they will do. There is rather wide agreement that the two-year goal, the first goal of lowering all tolerances to a negligible risk level is both appropriate public policy and do-able. And Commissioner Young acknowledged that.

The food industry and the agri-chemical industry and food processors are raising the issue of benefits because they view that as perhaps the only way to stop several hundred tolerances being lowered to a point where the product cannot be used. So from that side of the aisle, you are going to hear a lot of talk about benefits, and perhaps an overly aggressive standard.

On the other side of the issue are public interest and environmental groups that have looked at a record of EPA, which is not as strong as it could be in dealing with documented risks in the food supply. They have been dealing with ALAR for eight years, and it is still not resolved. All the fungicides that Senator Harkin noted, most of them have been under review for most of the 1980's and still essentially no steps have been taken to reduce the risks. So the public says EPA obviously must not be too concerned about these risks.

Their current program of re-registration and special review, as GAO and others have testified, will not come to closure until some time into the next century, which obviously is not acceptable. So these individuals look at the Delaney clause, the simple club of the Delaney clause, as about the only statutory provision with any hope of bringing about substantial reduction from pesticides in the food supply. And so they are very concerned about seeing this statutory tool compromised or weakened. When they hear a regulatory agency say, "We need more flexibility," they hear "No action." So you have got these two concerns working on both sides of the issue, and somehow in crafting legislation you are going to have to come up with a formulation that brings about, with a high degree of certainty, a large portion of risk reduction.

Our report estimated that you could eliminate 98 percent of the risk from the food supply with rather modest impacts on agriculture. And I would say that if you look at EPA's most recent analyses of those older pesticides, 90 percent is clearly within reach. This could be achieved in a year without legislation if they were to take action. With some modest amendments, the Kennedy bill could be crafted to force those actions, and we can get on with this problem.

The big concern and the problem that is going to, I think, pose the most difficulty for the committee is what to do about perhaps the last ten percent of risk, how strict a standard to use. I hope that the committee working with the agency can figure out a way to resolve this problem, and let us get the 90 percent that everyone agrees is there—we know what pesticides they are, and it is do-able within a very short amount of time—to eliminate that risk while additional statutory authority, better science, better enforcement is developed to deal with the remainder.

Thank you.

[The prepared statement of Mr. Benbrook along with responses to questions asked by Senator Kennedy follows:]

WILL S. 722 UNRAVEL DELANEY'S PARADOX?

PREPARED STATEMENT OF CHARLES M. BENBROOK, PH.D.

Mr. Chairman, I am delighted to have an opportunity to present testimony on S. 722, "Food Safety Amendments of 1989." My name is Charles M. Benbrook. I am the Executive Director of the Board on Agriculture of the National Research Council (NRC), National Academy of Sciences (NAS). I am accompanied today by my colleague, Mr. Richard Wiles, the staff officer in the NRC responsible for overseeing our work on pesticide regulatory issues, sustainable agriculture, and related matters.

In May of 1987 the NRC released a major report Regulating Pesticides in Food: The Delaney Paradox. We are pleased to note that several of the key provisions in S. 722 are based on our report's recommendations, and commend the Committee for taking action to resolve this perplexing and increasingly costly food safety dilemma. This morning I would like to highlight some of the major findings, conclusions, and recommendations of our report; identify provisions of S. 722 consistent with the report; note some aspects of the legislation that warrant further assessment, clarification, and possibly change; and, highlight a few critical food safety and pesticide regulatory policy issues that deserve the Committee's consideration.

Major Findings
of the 1987 NRC Report

The principal findings of our committee were:

- There are about 8,500 separate tolerances covering a residue of a distinct pesticide used on a distinct food crop--for example, captan residues in grapes.
- For 53 pesticides the Environmental Protection Agency (EPA) identified as of July 1986 as suspect oncogens, there are about 2,500 tolerances set under section 408 of the Food, Drug, and Cosmetic Act (FDCA) covering residues in raw agricultural commodities; and 31 tolerances for residues in processed foods set under section 409 of the FDCA.
- There are about 3,180 distinct processed food forms, each derived from a raw agricultural commodity on which a distinct pesticide may be used.
- The universe of pesticide uses possibly effected by the Delaney Clause includes over 800 processed food forms, each derived from a distinct crop on which one of some 55 oncogenic pesticides is registered for use.

- There are just over 30 section 409 tolerances covering concentrating residues of oncogenic pesticides in processed foods. These 30 plus tolerances all appear to violate the Delaney Clause. Moreover, these 30 tolerances are only a small fraction of the number that will be needed once more complete residue chemistry data is submitted to the EPA, particularly given how the Agency currently measures whether residues concentrate.
- Ten fungicides account for over half the estimated worst-case dietary cancer risk from residues on or in fresh food. Across all three major types of pesticides (herbicides, insecticides, fungicides), fresh foods account for about 80 percent of total worst-case risk, and processed foods about 20 percent.
- Residues of a dozen or so pesticides in or on 15 or 20 crops accounted for at least 90 percent of the total estimated worst-case risk.
- EPA has applied the Delaney Clause only to newer pesticides, even though older pesticides (those first registered before 1978) account for well over 90 percent of total worst-case dietary risk.
- EPA cites the Delaney Clause as the reason for denying registration of new pesticides posing worst-case cancer risks on the order of 10^{-7} to 10^{-8}, even though these new products would provide farmers a clearly safer alternative pesticide posing risks one hundredfold or more below the risk levels associated with currently registered products.
- Consistent adherence to a 10^{-6} negligible risk standard--applied to new and old products, all types of pesticides, and to the combination of residues in raw and processed foods derived from a particular use of a pesticide--would eliminate the vast majority (more than 90 percent) of worst-case estimated risk. To achieve this level of risk reduction, only 32 percent of all tolerances covering use of oncogenic pesticides--or about 750 tolerances--would need to be revoked. To eliminate the remaining 2 percent of risk, an additional 1,500 tolerances would have to be revoked.
- Strict and immediate adherence to the Delaney Clause would eliminate, at most, a little over half the current level of worst-case risk in the diet, through revocation of nearly 2,000 tolerances covering use of oncogenic pesticides on 38 different crops.

These findings and the committee's extensive deliberations on the challenges facing EPA in moving through the re-registration process on some 200 or more older pesticides used on food crops, led the committee to reassess the current statutory scheme and regulatory approach governing pesticide residues in food. Based on the committee's analysis, four major recommendations were offered. I attach the Executive Summary of our 1987 report, Regulating Pesticides in Food: The Delaney Paradox, which explains in more detail the analytical foundation of these findings and the committee's principal recommendations.

Recommendations of
the 1987 NRC Report

Our four principal recommendations are:

- A consistent standard should be applied to pesticide residues in raw and processed foods, to new and old pesticides, and to all types of pesticides.
- A negligible risk standard, applied consistently, could dramatically reduce risk with modest reduction of the benefits from the use of pesticides.
- "Logic argues that the EPA should focus its energies on reducing risk from the most worrisome pesticides on the most consumed crops, and compelling reasons support such a strategy." (page 14, Regulating Pesticides in Food: The Delaney Paradox)
- EPA should develop and apply improved analytical tools and a systematic approach to assessing dietary risks from pesticides.

Major Provisions of S. 722

S. 722 is a complex, comprehensive bill that goes well beyond the recommendations in our 1987 report. It is an ambitious bill in that it strives in a relatively short period of time to remove nearly all dietary risk both from pesticide active ingredients and pesticide product inert ingredients. (Under the provisions of S. 722, the task of dealing with inert ingredients could pose considerable drain on Agency resources, and would direct attention away from other challenges such as pesticides in ground water and developing scientifically sound regulatory principles to assess the safety of pest control technologies evolving from recombinant DNA techniques.)

As the Committee considers amendments to S. 722, attention should be directed to the administrative feasibility and cost of the bill's major provisions, with a special focus on perfecting and passing those sections of the bill that would bring about substantial risk reduction without posing potentially large costs on farmers, the regulated industry, EPA, and society as a whole.

Two key provisions of S. 722 are consistent with the NRC report's recommendations:

- The existing statutory inconsistency is resolved between the tolerance-setting standards established in section 408 and section 409 in a direct, and common sense approach.

- A negligible risk standard is proposed, and applied consistently to all pesticides.

While conceptually consistent with several key aspects of the 1987 NRC report, S. 722 would bring about an even more rapid and dramatic reduction in risk than a regulatory strategy patterned after the committee's basic recommendations. Recall that our recommendations, if fully adhered to, would eliminate 95 percent or more of the oncogenic risk posed by pesticide residues in the diet. Two central features of S. 722 warrant further consideration.

- When setting tolerances consistent with a negligible risk standard, the bill requires EPA to consider unique risks faced by vulnerable population groups (infants, children, pregnant women, the ill), and people who may consume relatively larger quantities of particular pesticides because of unusual dietary patterns.

A possible problem in requiring EPA to consider risks faced by infants and children is that EPA lacks the scientific knowledge base to do so. As written, S. 722 can be interpreted to require EPA to postpone tolerance adjustments until new scientific methods are developed and new toxicology data is generated by registrants. As an alternative, the Committee might direct EPA to set tolerances at levels consistent with a negligible risk standard, based on currently available data and prudent risk assessment methods.

Developing sound risk assessments methods for special population groups will take several years, since EPA still is uncertain about what new studies to require. Indeed, the NRC is currently undertaking a major study, mandated by Congress and supported by EPA, on how to incorporate in the pesticide regulatory process the unique consumption patterns and toxicological susceptibility of infants, children, and pregnant women. (See attached description of this committee's mandate and activities.) Our ongoing study is a first step in a process bound to take at least a decade.

- The bill requires that the combined risk from all uses of a pesticide meet the negligible risk standard in four years. Our committee found that a crop-wide approach (e.g., all fungicides registered on a given crop) to regulation is a more effective, reliable way to reduce risk. Accordingly, the committee recommended to EPA that pesticide risks and benefits should be estimated for each distinct crop, across all pesticides of the same type registered for use on the crop (for example, fungicides registered for use on peaches, herbicides used on soybeans).

Several problems could arise as a result of the four-year goal under S. 722. It would be administratively difficult to determine how to meet the goal. It would place the Agency in an awkward position where it would have to choose which crop uses to spare and which to cancel. It could conceivably penalize chemicals with many uses, and might exacerbate the loss of minor use registrations under re-registration. It could set back efforts toward Integrated Pest Management (IPM), an approach to pest control that can dramatically reduce overall reliance on pesticides, but does so in part through judicious, occasional use of a wide range of pesticide products. Attempts to slow the emergence of pesticide-resistant pest populations would be made more difficult in some instances. To meet the four-year goal, EPA would, in all likelihood, have to cancel many additional tolerances for at best marginal additional gain in public health protection. The bill's six-year risk reduction goal would exacerbate many of these potential problems.

Critical Questions Before the Congress and the Public

Several key policy issues should be addressed thoughtfully as food safety reform legislation is developed by the Committee. Some questions reflect the role of benefits in regulatory decisionmaking, others arise from the imperfect art of risk assessment--most regulatory actions are now based upon very crude estimates of human risk. In most instances, current models and data over-estimate human risk, but in other cases, possibly significant sources of risk may be missed. In addition, significant data gaps persist, and science is just beginning to consider additional biological endpoints--neurotoxicity, and immological effects are two examples.

The Appropriate Standard and How to Apply It to Both New and Old Pesticides.

The effectiveness and cost of S. 722 will be determined, in large part, by how it defines and applies negligible risk, at what level a negligible risk standard is set, and what EPA is required to do (and how fast) to reduce existing tolerances that currently could pose risks above a negligible level.

Pesticide residues in the diet are often the most worrisome result of a pesticide's use. In other cases, worker exposure, wildlife impacts, or groundwater contamination may be the Agency's greatest concern. By tightening down aggressively and exclusively on dietary risks, full implementation of the provisions of S. 722 as written will lead to the cancellation of many pesticide uses, some of which may pose rather marginal dietary risks. As a result, farmers will have to switch to other products or technologies, which may pose other, more serious risks. The loss of several hundred major uses of the 10 registered oncogenic fungicides could prove particularly worrisome, since it is unclear how quickly farmers could adapt, or whether the public would face greatly elevated risks from natural molds, fungi, and toxicants which would be more difficult to keep in check.

Procedural Inconsistency With the FIFRA Status

Our 1987 report addresses the need to eliminate inconsistency between the standard governing the setting of tolerances under FIFRA (risk-benefit) and section 409 (Delaney Clause zero-risk). S. 722 would resolve this inconsistency, but inadvertently creates a possibly significant procedural inconsistency. Tolerance reductions mandated by S. 722 will clearly have to be accompanied by changes in some pesticide product labels. Labels are what govern lawful pesticide use, and are the critical link between farmers and applicators, and attainment of public health and environmental protection goals.

Label changes that involve restricting the number of applications, rates of application, or pre-harvest intervals, however, must be made following the administrative procedures and risk-benefit standards in FIFRA. Through amendments to the FDCA, S. 722 will compel EPA to reduce tolerance levels in several hundred cases as a necessary step to save a registration. In some of these cases, accompanying label changes will be essential in order to keep actual residues on or in food below the now lowered tolerance levels. Yet, EPA must base such label changes on a risk-benefit determination, thereby triggering the complex, time-consuming procedures inherent in the FIFRA statute. Regrettably, EPA lacks statutory authority under FIFRA to reduce tolerances in an administratively expeditious fashion. The obvious remedy to this situation, possibly as a companion bill or amendment to S. 722, is a new section in FIFRA providing EPA conditional risk reduction authority, patterned after the Agency's current authority to grant conditional registrations. (Conditional registration authority allows EPA to grant a registration "conditionally," pending receipt of additional data. Congress granted EPA this authority to lessen the time period needed to gain new product registrations.)

The need for conditional registration in the late 1970s is matched in the late 1980s by the need for conditional risk reduction authority, coupled with a more expeditious suspension/cancellation process. To resolve potential procedural problems following passage of S. 722, Congress must somehow work around or overcome long-standing jurisdictional tensions that arise when Congress attempts to harmonize and/or modernize environmental and public health protection policies in the FIFRA and FDCA statutes.

The Role of Benefits and How to Calculate Them

Events in recent months highlight the difficult public policy issues that arise in the context of considering benefits in pesticide regulatory decisionmaking. S. 722 would eliminate consideration of benefits when risks are above a negligible level. This change in policy would greatly simplify the regulatory process, and provide EPA new authority to act decisively in reducing tolerances when data shows a pesticide might pose risks above a negligible level. It is important to note that S. 722 does not eliminate consideration of benefits in all cases, an erroneous claim that arose repeatedly in hearings before Congressman Henry Waxman's subcommittee.

If the negligible risk standard is defined and applied as proposed in S. 722, the lack of any consideration of benefits becomes more worrisome to farmers and the food industry, who fear the prospect of losing many, perhaps most uses of the approximately one-third of currently registered food use pesticides that pose some level of oncogenic risk. This may not sound threatening to the Committee or the public, since there would still be many products available. The problem, however, is the prospect of major changes in our ability to produce several major fruit and vegetable crops, foods that we all need to eat more of to meet dietary goals (see the recently released NRC report Diet and Health). Production of these crops in humid regions in the southeast, mid-Atlantic, and northeastern states would become difficult to sustain, unless there are dramatic and unanticipated developments in application of genetic engineering and biological pest control.

The impact of S. 722 on other farmers' ability to control pests would be, for most of American agriculture, modest. But for a few crops, in a few regions, in certain years, the impact would clearly be of major concern. In some cases, crop yields would decline, raising per unit costs. In other cases, farmers would be unable to protect produce and fruit from certain diseases and pests that blemish or scar the surface of fruit or vegetables. This loss of quality would drive down prices, unless consumer attitudes change, and could increase natural sources of risk in the diet.

These considerations raise the need to revisit the role and definition of benefits in pesticide regulation. What sorts of benefits should be taken into account? How should they be measured?

The 1987 NRC report did not speak directly to this issue. If and when benefits are considered, many people argue that they should be defined more broadly. Ideally, the assessment of benefits should not stop at the farmgate, as is currently the case for all intents and purposes. The net benefits of alternative pest control strategies--chemical and non-chemical--should be estimated, taking into account the cost and availability of food, the ability to supply fresh fruits and vegetables year-round (a key factor in building consumer acceptance), the potential risks of pesticides and natural toxicants from food produced overseas or grown in this country without effective control measures, the cost of public and private efforts to assure and monitor the safety of the food supply (already several hundred million annually, growing fast with no end in sight), and the prospective direct and indirect costs of human health problems likely to result from registered uses of pesticides (both acute and chronic problems in manufacturing plants, on the farm, among farmworkers, people drinking contaminated water in certain farming regions, and the general public).

In defining the role for benefits in pesticide regulatory decisionmaking, the Congress should assess realistically the cost and feasibility of carrying out benefits assessments. Given current methodologies and data for making such estimates, it could be both contentious, and certainly will be costly to estimate pesticide use benefits in a way which is analytically sound. Does it make sense to invest more heavily in learning how to estimate pesticide benefits for several thousand uses of old pesticides in an era when funding is almost non-existent for research on the biological control of pests, the adoption of proven Integrated Pest Management systems, and non-chemical alternatives to pesticides? I hope Congress will ponder this key question of priorities and public policy.

In closing, I would like to stress that S. 722 is ambitious, comprehensive, and carefully drafted legislation. While a number of potential problem areas have been noted, rather modest changes in S. 722 could largely alleviate these problems. It is assuredly far more important for the Congress to perfect and pass this legislation than proceed toward passage of legislation banning Alar, the latest but not last pesticide to gain national attention. The decision last week by the manufacturer of Alar to suspend sales until safety issues are resolved lessens the need for Congress to ban this product through legislation. Hopefully, the Congress will now focus its attention on S. 722.

Thank you for the opportunity to speak before the committee this morning. I commend you and the Committee for taking on this politically contentious task.

REGULATING PESTICIDES IN FOOD

THE DELANEY PARADOX

Executive Summary

In February 1985, the Environmental Protection Agency (EPA) asked the Board on Agriculture of the National Research Council to study the EPA's methods for setting tolerances for pesticide residues in food. Specifically, the EPA asked the board to examine the impact of the Delaney Clause on the tolerance-setting process. Although the Delaney Clause appears on its face to be a minor feature of the complex statutory scheme governing the regulation of pesticides and pesticide residues in food, its potential impact on the EPA's future decision making is great.

The EPA establishes tolerances for pesticide residues on raw commodities under section 408 of the Federal Food, Drug and Cosmetic (FDC) Act. Enacted in 1954, this law stipulates that tolerances are to be set at levels deemed necessary to protect the public health, while taking into account the need for "an adequate, wholesome, and economical food supply." Section 408 thus explicitly recognizes that pesticides confer benefits and risks and that both should be taken into account in setting raw commodity tolerances.

Pesticide residues that concentrate in processed food above the level authorized to be present in or on their parent raw commodities are governed by the FDC Act's section 409, the law governing food additives. Under section 409, such residues must be proven safe, which is defined as a "reasonable certainty" that "no harm" to consumers will result when the additive is put to its intended use. Consideration of benefits is not authorized. Moreover, section 409 contains the Delaney Clause. This clause prohibits the approval of a food additive that has been found to "induce cancer" (or, under the EPA's interpretation, to induce either benign or malignant tumors—i.e., is oncogenic) in humans or animals.

The dichotomous statutory standards applicable to tolerance setting inspired this study. A pesticide regulated on a risk/benefit basis at the time of registration and in the setting of tolerances for residues in or on raw agricultural commodities becomes, solely because it concentrates in processed food, subject to the Delaney Clause's ostensible zero-risk standard. This shift in criteria has potentially far-reaching effects. If any portion of a crop to which an oncogenic pesticide has been applied is processed in a way that will concentrate residues, the EPA's current policy is to deny not only a section 409 tolerance for the processed food but also a section 408 tolerance for residues of the pesticide in or on the raw commodity. Further, if required section 408 tolerances cannot be granted for a food-use pesticide, the EPA must also deny registration of the pesticide under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

The EPA's policy concerning application of the Delaney Clause to new pesticides and new uses is fairly clear. The EPA's policies are currently less settled regarding the large number of already-registered pesticides, however, and are expected to come under intense pressure in coming years. The sources of this pressure are the following:

- The EPA has instituted programs to expand substantially the data on the toxicological properties of pesticides and the tendency of individual pesticides to concentrate in processed foods.
- Once tested in accordance with contemporary standards, many older pesticides are likely to be identified as oncogenic or potentially oncogenic, inviting regulatory action by the EPA.
- As more data on the tendency of pesticides to concentrate in processed food become available, many more currently registered pesticides will be shown to need section 409 tolerances and thus will become subject to the Delaney Clause.

It is unlikely that the EPA will be able to avoid applying the Delaney Clause to registered pesticides. Thus, as the agency proceeds through the reregistration process, it must determine how to apply the zero-risk standard of the Delaney Clause to a significant number of currently registered, commercially important pesticides. Because of the potential magnitude and complexity of this task, the EPA asked the Board on Agriculture to undertake this study.

The committee undertook three principal tasks. First, it examined the statutory basis of tolerance setting for pesticide residues in food and the operation of the tolerance-setting process at the EPA. Second, it developed a computerized data base to estimate the potential dietary oncogenic risk associated with pesticides determined or suspected by the EPA to be oncogenic. Third, using the data base it had developed, the committee analyzed the impact of alternative approaches to tolerance setting on estimated cancer risks and pesticide use and development.

THE COMMITTEE'S ESTIMATES OF ONCOGENIC RISK

The analytical methods involved in estimating oncogenic risks from pesticide residues in food contain many areas of scientific and technical uncertainty. The assumptions made to account for these uncertainties can have profound implications for the resulting risk estimates. For example, the calculation of exposure to pesticide residues in a given foodstuff can yield risk estimates that vary by an order of magnitude. The committee assumes all residues are at the tolerance level, although actual residues may be different. Likewise, assumptions regarding how and when to aggregate risks from a pesticide used on a variety of crops can significantly alter risk estimates. The quantification of a pesticide's oncogenicity potency, called a Q star or Q*, can also vary by orders of magnitude, depending on such factors as whether a surface area or body weight correction is made in extrapolating risks from rodents to humans, the choice of extrapolation model, or whether malignant and benign tumors are combined when calculating the response to a given dose. The Q*'s used by the committee were calculated by EPA scientists and have not been formally peer reviewed.

The EPA generally follows a conservative policy in estimating risk. Whenever assumptions must be made, the agency attempts to make them in a way that minimizes the chance of underestimating risks. The cumulative result of these assumptions is an upper-bound estimate of additional oncogenic risk above the background cancer risk of 1 in 4 or 0.25 (2.5×10^{-1}). For perspective, it is worth noting that an additional dietary oncogenic risk of 1 in 1 million or 1×10^{-6} would raise this background risk of 0.25 to 0.250001. In developing the risk estimates contained in this report, the committee adopted what it understood to be the EPA's current methodology for quantitative risk assessment, recognizing that many key elements of the agency's risk assessment procedures are under review. This report only notes the importance of these assumptions and underlying issues; it does not offer resolutions.

In arriving at a regulatory position on an oncogenic pesticide, the EPA considers the relative significance of all the evidence of oncogenicity for a compound. This "weight-of-the-evidence" approach involves considering many qualitative factors such as the tumor type, results of mutagenicity bioassays for the compound, and negative oncogenicity test results. In calculating the distribution of dietary oncogenic risk and the consequences of regulatory scenarios examined in this report, the committee did not use weight-of-the-evidence techniques. Instead, it relied entirely on the quantitative risk assessment methods that the EPA uses. Risk estimates are generally shown with the EPA's oncogenic classification for the compound, however. This classification system is designed to characterize a pesticide's oncogenicity in humans (see Chapter 3).

The reader should understand that a wide margin of uncertainty surrounds nearly all of these numbers. With this in mind, the reader should focus on general patterns of risk distribution and how key parameters change when policy alternatives are assessed, not on specific point estimates of risk.

The committee further emphasizes that all risk estimates in this report are limited to oncogenic risk from pesticide residues in food. This does not imply, however, that other risks presented by pesticides or other routes of exposure are less important. Indeed, the regulation of pesticides involves a consideration of many health and environmental risks, only one of which involves residues of oncogenic pesticides in food.

ESTIMATED ONCOGENIC RISK AND ITS DISTRIBUTION IN THE FOOD SUPPLY

To characterize the universe of oncogenic pesticides, the committee adopted the list of 53 suspected oncogenic compounds that the EPA transmitted to Congressman Henry Waxman (D-Calif.) in October 1985. Of these compounds, the committee limited its analysis to three types of pesticides—herbicides, fungicides, and insecticides. The risk estimates discussed in this report are derived from only 28 of these 53 active ingredients (see Chapter 3). To roughly characterize the benefits associated with the use of these oncogenic compounds, the committee assembled crop use and farm-level expenditure estimates averaged over three years on all 53 compounds.

Findings

The committee's analysis indicates that the Delaney Clause will be central to the EPA's decision making in future years.

First, the EPA considers a substantial fraction of all herbicides, fungicides, and insecticides to be oncogenic or potentially oncogenic in animal studies. On the basis of pounds of pesticide applied, 60 percent of all herbicides are oncogenic or potentially oncogenic. (This number includes two compounds not on the "Waxman list" that have since been found to be suspect oncogens, raising the percentage from around 40 percent to just over 60 percent.) By volume, 90 percent of all fungicides fall into this category, as do about 30 percent of all insecticides.

Second, for the 53 oncogenic compounds, the committee has identified 31 processed foods with approved section 409 tolerances. All of these appear to conflict with the Delaney Clause. Moreover, the committee has identified an additional 778 processed foods *with no 409 tolerances* for which oncogenic pesticides are registered. Residues of these pesticides are expected to concentrate in many of these processed foods. Hence, over the next few years, the EPA will face bringing several hundred additional pesticide uses into compliance with section 409 of the FDC Act and the Delaney Clause.

Third, over the next five years, the EPA is scheduled to complete regulatory actions that will force decisions on compliance with the Delaney Clause for 10 currently registered oncogenic pesticides. These pesticides account for between 80 and 90 percent of the total estimated dietary oncogenic risk from residues of the 28 compounds that comprise the committee's risk estimate (see Chapter 3).

Fourth, the committee explored the distribution of dietary oncogenic risk from residues of these 28 pesticides. Fungicides account for about 60 percent of all currently estimated dietary oncogenic risk from these 28 compounds. Of the remaining risk, 27 percent stems from crop uses of herbicides and 13 percent from insecticides. Fungicides, however, account for only about 7 percent of all pesticide sales and less than 10 percent of all pounds applied. Further insights derived from the committee's analyses of these 28 pesticides include the following:

- About 55 percent of the total estimated dietary oncogenic risk stems from residues on crops that have raw and processed food forms.
- About 20 percent is associated with consumption of the processed forms of these crops. Approximately 35 percent is from consumption of the raw form of the same crops.
- About 45 percent of estimated dietary oncogenic risk is from foods that the EPA considers to have no processed form. These foods include many fruits and vegetables and *all* meat, milk, and poultry products.

These figures lead to several observations:

- At most, the Delaney Clause could apply to processed-food residues responsible for only one-fifth of the estimated dietary oncogenic risk from pesticides. However, its implementation could eliminate another 35 percent of the estimated risk from residues on the raw forms of these processed foods because it is the EPA's policy to deny section 408 raw food tolerances when section 409 tolerances cannot be established for the processed forms of the same crop.

- Foods accounting for nearly one-half of the total estimated dietary risk (all meat, milk, poultry, and pork products and many fruits and vegetables) are ostensibly beyond the scope of the Delaney Clause, because under current EPA guidelines they have no processed form.

Fifth, dietary oncogenic risk appears to be concentrated in a relatively small number of pesticides and crops. Nearly 80 percent of the estimated dietary oncogenic risk (from all 178 food uses of the 28 compounds that comprise the committee's risk estimate) is from residues of 10 pesticides on only 15 different foods.

IMPACTS OF FOUR ALTERNATIVE WAYS TO REGULATE ONCOGENIC RESIDUES

The committee studied the implications of four theoretical policy scenarios, or frameworks, for regulating residues of oncogenic pesticides in food. The committee emphasizes that these scenarios are artificial constructs chosen not because they reflect any current regulatory approach but rather because they represent a plausible range of approaches. Further, the committee does not offer a legal opinion on the compatability of any of these scenarios with current law or interpretation. These tasks were not in the committee's charge.

Scenario 1 applies a zero-risk standard for oncogenic risk to all pesticide residues on both raw and processed foods. If the EPA determined that a pesticide was oncogenic, all food tolerances for that pesticide would be revoked.

Scenario 2 applies a zero-risk standard for oncogenic risk to all pesticide residues in *processed* foods: any residue of an oncogenic pesticide in a processed food would be disallowed. This scenario further assumes that when residues of an oncogenic pesticide are present in the processed portion of a crop, tolerances for both raw and processed forms would be revoked.

Scenario 3 would revoke all tolerances for a pesticide on a crop when the combined estimated cancer risk from the residues of that pesticide on both the raw and processed forms of a crop exceeds 1 in 1 million or 1×10^{-6}.

Scenario 4 would revoke all tolerances for a pesticide on a crop when the total risk from residues of a pesticide on all *processed* forms of a crop exceeds 1×10^{-6}. As under scenario 2, when residues on the processed form of the crop trigger revocation, both raw and processed food tolerances would be revoked.

Results of the Scenarios

Scenario 1 would revoke all tolerances for all oncogenic pesticides and eliminate all estimated dietary oncogenic risk.

Scenario 2 would revoke tolerances that would reduce dietary oncogenic risk (from the 28 pesticides that constitute the committee's estimate of dietary oncogenic risk) by 55 percent, ignoring about 45 percent of total estimated dietary risk from foods with no processed form.

Scenario 3 would reduce total estimated risk from these 28 compounds by 98 percent, while revoking only 32 percent of all tolerances for the 28 oncogenic pesticides.

Scenario 4 would eliminate just 35 percent of the estimated dietary oncogenic risk, while revoking the smallest percentage of all tolerances.

The most significant finding from the committee's crop level analyses is that under a "negligible risk" standard applicable to residues on both raw and processed food—illustrated by scenario 3—a high percentage of total risk is eliminated while a low percentage of "benefits" (as measured here by acre treatments and expenditures) are lost. For certain crops, scenario 4 would also eliminate a high percentage of total risk while affecting a low percentage of benefits. Scenario 4 would be less effective at reducing overall risk, however, by not addressing tolerances on three of eight crops.

Scenarios 1 and 2 have the same effect on all crop-pesticide combinations examined except peanut fungicides; all oncogenic risk from residues on these crops would be eliminated. In most cases, tolerances associated with a significant percentage of current pesticide expenditures and acre treatments on these crops would be lost. For certain crops in certain regions, the loss of all oncogenic compounds—particularly fungicides—would cause severe short-term adjustments in pest control practices because of the lack of economically viable alternatives.

Findings

The four scenario analyses suggest that progress toward risk reduction could be the greatest and most uniform when raw and processed foods are subject to a consistent risk standard. The potential advantages of a negligible risk standard, with no consideration of benefits, are also highlighted. Such a standard, consistently applied, could eliminate most existing dietary oncogenic risk while allowing continued use of—and benefits from—certain low-risk compounds.

AN ANALYSIS OF THE FUNGICIDES: A SPECIAL CASE

Fungicides present a unique problem. The EPA needs to establish hundreds of new processed-food tolerances for these compounds, but about 90 percent by weight of all fungicides now applied are considered potential oncogens. All but 1 of the 14 oncogenic fungicides were registered more than 15 years ago. These older pesticides are relatively inexpensive, remain effective in various applications, and provide significant benefits to agricultural producers and consumers. These fungicides are important in the production of many high-value fruit and vegetable crops, particularly in the eastern and southeastern regions of the country. The eleven fungicides in the committee's total risk estimate represent less than 10 percent of all acre treatments with pesticides, but are responsible for about 60 percent of the total estimated dietary oncogenic risk.

The mode of action of fungicides makes it difficult to develop compounds that are nontoxic to genetic material. As a result, few effective non-oncogenic new fungicides are being developed. Only four fungicides registered since 1972 have gained greater than 5 percent of the market share for any food crop. Data on several of these compounds indicate oncogenicity and other chronic effects, however.

The combination of the above factors makes the regulation of oncogenic risk from fungicide residues extremely complex. It is the committee's view that literal application of the Delaney Clause will significantly complicate the EPA's efforts to reduce dietary oncogenic risks from fungicides. The committee performed several simple analyses (see Chapter 5) showing that sequential tolerance revocations or denials for one active ingredient at a time could in some cases actually *increase* human dietary oncogenic risk and in many other cases only lower it slightly. These results would occur when the use of a fungicide presenting an equal or greater risk *increased* after tolerances for a less-hazardous compound were revoked.

In response to this dilemma, the committee examined the effect of cropwide tolerance reductions as a means for reducing estimated dietary risk from fungicides. Even a cursory analysis suggests that this and other new regulatory strategies warrant detailed study in terms of their potential to bring about significant reduction in dietary oncogenic risk while preserving beneficial fungicide uses. Cropwide tolerance reductions could reduce the total estimated dietary oncogenic risk from fungicides by up to 50 percent with only modest enforcement effort and minor adjustments in the agricultural sector.

PESTICIDE INNOVATION AND ALTERNATIVE PEST-CONTROL METHODS

Despite the development of pest resistance to chemical pesticides, environmental damage, applicator risk, and fears of cancer associated with pesticide use, most farmers believe that pesticides are a critical part of a reliable and cost-effective pest control strategy. If a large number of tolerances for oncogenic pesticides are revoked over the next five years, adequate replacement pesticides, particularly fungicides, probably would not be available for several major fruit and vegetable crops. For herbicides, however, the prospects are more optimistic. Considering all alternatives being developed, it appears that the loss of several major oncogenic herbicides would not pose a serious threat to agriculture. The outlook for insecticides lies somewhere between that for herbicides and fungicides.

The simultaneous loss of several oncogenic fungicides as described above could present serious disease control problems in certain crops in major production regions. Further, the rate of successful new product development within the three major categories of pesticides is almost inversely proportional to dietary risk; innovation has not been occurring to address the problem of oncogenicity.

Alternative Technologies

Advances in classical plant breeding, innovation in biological and cultural pest control systems, and progress in genetic engineering offer some promise for nonchemical pest control in the future. Nonchemical approaches will be encouraged by tolerance revocations if more profitable chemical controls are not available. For many crops, especially fruits and vegetables, there are few equally effective technologic alternatives to chemical pest control. More important, as with synthetic chemical pesticides, R&D efforts in alternative technologies do not appear directed toward the pest problems most likely to be affected by Delaney Clause-driven tolerance revocations; breeding for disease resistance is an important exception.

Because of the time needed to further develop plant genetic engineering techniques, new technologies involving or derived from biotechnology will not be available to reduce the impact of the next five years of regulatory actions. Although plant breeding offers the promise of more pest-resistant crop varieties, these new varieties will probably lower rather than eliminate the need for pesticides. The objective of biocontrol techniques is to establish a more stable pest control situation in the long run, but these methods are often complex and do not always provide the certainty that chemical pesticides provide. The problems with these alternative technologies will delay the adoption of nonchemical techniques in the absence of incentives.

The Effect of the Delaney Clause on R&D

In the long term, a rigorous application of the Delaney Clause to both existing and new pesticides is likely to shift the focus of public and private

R&D away from oncogenic compounds and reduce the total investment in chemical pesticides. This shift and reduction of investments will depend on factors that the committee was not able to examine quantitatively, including the structure of the industry (corporate mergers), regulatory developments, and scientific breakthroughs. If gross sales of agricultural chemical companies are reduced or if net returns become more variable as a result of tolerance revocations, however, revenues available for these R&D activities will decline and overall innovation is likely to fall. These declines in R&D investments are more likely if revocations lead to increased use of nonchemical controls—developments that provide no profit for pesticide companies.

The Minor Use Issue

All fruit and vegetable crops grown in the United States are considered "minor" crops in terms of pesticide use. Most minor crops have no recognized processed forms under EPA regulations. Most minor crops also present relatively small oncogenic risks. The important issue with these crops is whether pesticides currently vital to their production will remain available when the tolerances for oncogenic pesticides on other crops are revoked pursuant to the Delaney Clause.

Certain minor crops with processed forms *do* present potentially significant risk, however. Apples, tomatoes, grapes, potatoes, and citrus are directly vulnerable to tolerance revocations under any version of the Delaney Clause. In contrast to most minor crops, these crops represent intermediate markets for pesticide producers and therefore provide an incentive for product development. In this fashion, the continued availability of pesticides for small minor crops is linked to the continued availability of pesticides on "minor" crops representing larger markets.

Liability for crop failures or crop injury is another potential obstacle to future pesticide availability for small minor crops. This results from the limited acreage of these minor crops and hence the limited pesticide market they provide, relative to potential liability for control failures. Liability is high because these crops have high per acre value and must meet high-quality standards.

The Delaney Clause and Pest Resistance

A distinct value of many widely applied, suspect oncogenic fungicides is that even after years of use, pests show little if any resistance to them. In contrast, a number of pests have developed some degree of resistance to many of the new, non-oncogenic or more weakly oncogenic fungicides and insecticides. The viability of many of these newer compounds is often linked to their simultaneous use with the older oncogenic compounds. Given the large number of tolerances for older fungicides that may be revoked under the Delaney Clause, there is a critical need to develop non-oncogenic fungicides as well as resistance management programs for these fungicides in the next five years.

MAJOR CONCLUSIONS AND RECOMMENDATIONS

The committee's analysis and findings support four basic conclusions. The first deals with the legal and institutional base for regulating oncogenic pesticide residues in food. The second addresses the possible roles of other than zero oncogenic risk criteria in targeting regulation on pesticide uses that pose potentially significant human health hazards. The third involves the need for and structure of an overall strategy for the EPA as it moves ahead with the task of bringing all existing pesticide registrations and tolerances into compliance with the law, including the Delaney Clause. The fourth describes the adoption of an analytical framework to facilitate a more systematic examination of the risks and benefits associated with pesticides.

Legal Basis for Regulation

Pesticide residues in food, whether marketed in raw or processed form or governed by old or new tolerances, should be regulated on the basis of consistent standards. Current law and regulations governing residues in raw and processed food are inconsistent with this goal.

First, the committee can discover no scientific reason for the law's different treatment of raw and processed food tolerances. Because the committee could find no scientific reason for this disparity, it recommends the consistency and simplification of treating them alike.

Second, residues stemming from the use of older pesticides should be subject to the same scrutiny and standards as those applied to residues from new pesticides. Although concentrating on new pesticides that might present new dangers was a reasonable policy when the regulation of pesticides began, new analyses, data, and criteria provide compelling reasons for uniform treatment of old and new compounds. Neither the FDC Act nor FIFRA provides a clear basis for treating residues of new pesticides differently from those of old pesticides. Subjecting old tolerances to contemporary safety criteria is essential.

The committee's analysis demonstrates that about 90 percent of estimated dietary oncogenic risks from pesticides stems from uses sanctioned by tolerances granted before 1978. The only way for the EPA to reduce dietary risk substantially is to subject old pesticides to the same regulatory scrutiny it applies to new agents. Doing so in the context of reregistration will provide the EPA with an opportunity to reduce public exposure to at least some of the oncogenic pesticides that now are routinely present in food.

Third, the two agencies charged with implementing and interpreting the Delaney Clause—the EPA and the Food and Drug Administration (FDA)—should continue to work to achieve consistent legal interpretations of their common statute and compatible regulatory policies based on the best contemporary science. As long as the Delaney Clause is a part of the FDC Act, better cooperation and communication between EPA and FDA scientists and policy-level officials will be increasingly important as the two agencies work to develop policies for implementing this provision. The effective functioning of both agencies depends on the development of consistent policies for achieving the widely supported goal of eliminating added carcinogens from the food supply whenever feasible and prudent.

A Nonzero Standard for Oncogenic Risk

A negligible risk standard for carcinogens in food, applied consistently to all pesticides and to all forms of food, could dramatically reduce total dietary exposure to oncogenic pesticides with modest reduction of benefits.

The committee believes that the elimination of oncogenic pesticide residues from human food is an appropriate aspiration of regulation. The committee recognizes, however, that residues of several dozen oncogenic pesticides may be found in hundreds of different foods. Many such residues pose little risk to humans, whereas some clearly warrant attention and, quite probably, regulatory action. The problem of implementing action against many pesticides with limited personnel and resources should be minimized. Moreover, the challenge for regulators grows increasingly complex as science and technology advance. Improvements in analytical chemistry and residue detection capabilities, new toxicological data, changing pesticide use practices, and the development of new pesticides and foods establish an urgency *and* the feasibility to devise a strategy for attaining a safer food supply.

One option for regulators is to adopt a negligible risk standard in setting and revising tolerances for all oncogenic pesticides found in food. The committee sees merit in such a standard *if* its adoption can speed up progress toward risk reduction and help the EPA focus its limited resources on pesticides and crops that pose significant oncogenic risks.

The committee notes with concern that current EPA policy has allowed continued use of pesticides that pose estimated dietary oncogenic risks as high as 1 in 10,000 (1×10^{-4}). The adoption of a negligible-risk standard would provide added justification for the agency to reduce relatively high risks while deferring actions on relatively low or perhaps even zero risks. The committee would not endorse the adoption of such a standard if it were not consistently applied to all pesticides and all forms of human food.

The committee is aware that a zero-risk standard applied to pesticide residues in all foods would eliminate that source of oncogenic risk in the diet. The committee believes, however, that in certain regions and on certain crops, the implementation of such a policy would cause severe adjustments in agricultural practices, particularly in control of plant diseases. This policy could impede agency discretion necessary to achieve significant risk reduction over the next 5 to 10 years while maintaining viable disease control alternatives.

The committee's analysis highlights several advantages of a consistently applied negligible-risk standard over even strict adherence to the traditional zero-risk interpretation of the Delaney Clause, which applies a zero-risk standard only to processed foods and their parent raw commodities:

- The committee found that, if consistently applied, a negligible-risk standard applied to raw and processed foods (assuming no consideration of benefits) could lead to the elimination of 98 percent of existing dietary risk from exposure to the 28 pesticides comprising the committee's estimate of dietary oncogenic risk. In contrast, a zero-risk standard applied only to oncogenic residues in processed foods and their parent raw commodities would reduce estimated risk by just 55 percent. In reality, however, benefits must be considered, and not all residues will concentrate. Also, the risk reduction achieved under both scenarios will probably be less than suggested. Nonetheless, the committee believes that the relative effectiveness of these two scenarios will remain constant and that any plausible negligible-risk standard that treats section 408 and 409 tolerances consistently will lead to greater risk reduction than a zero-risk standard applied only to section 409 tolerances.
- A uniform negligible-risk standard could give the EPA the flexibility needed to reduce dietary oncogenic risks over time. One important option would be the ability to grant tolerances for new chemicals that might pose a slight oncogenic risk (currently prohibited by the Delaney Clause), if use of such pesticides would displace more hazardous products now routinely used. In the past, the EPA has applied the Delaney Clause to deny tolerances for weak oncogens on certain crops. To date, the agency has not invoked the clause to revoke any existing tolerances (in most cases

citing lack of acceptable data on oncogenicity and residue concentration). This application of the Delaney Clause has had the effect of preserving the market share for, and continuous dietary exposure to, pesticides that present relatively greater dietary oncogenic risks.

- A negligible-risk standard for tolerance setting would aid the EPA in focusing regulatory resources on the crop and pesticide combinations presenting the greatest oncogenic risk. On the other hand, a zero-risk standard does not encourage and may not allow the EPA to discriminate between relatively significant and relatively insignificant oncogenic risks. Indeed, the Delaney Clause has focused considerable agency resources on protracted scientific assessments designed to determine whether a pesticide is an "oncogen" per se and whether the risk associated with a particular use of that pesticide is zero, or some very small level that is well beyond the predictive power of currently available toxicological tests and risk assessment methods.

The advantages of a consistently applied negligible-risk standard will depend on how fast the EPA will reregister old chemicals, the sequence that will be followed, and perhaps most important, how the benefits will be taken into account. Risk reductions of the magnitude that the committee's analyses suggest are not guaranteed because the analyses did not incorporate benefit considerations. The benefits of some pesticide uses may justify greater risks. The level of risk reduction achieved through the adoption of such a negligible-risk standard will depend on the importance the EPA places on the benefits of specific pesticide uses.

Targeting High-Risk Pesticide and Crop Uses

The committee's analysis (described on pages 50–66) suggests that about 80 percent of oncogenic risk from the 28 pesticides that constitute the committee's risk estimates is associated with the residues of 10 compounds in 15 foods. Logic argues that the EPA should focus its energies on reducing risk from the most worrisome pesticides on the most-consumed crops, and compelling reasons support such a strategy.

First, if the EPA developed a regulatory position on all oncogenic pesticides used on a given crop, the agency would have a realistic chance of dealing with the special problems that arise when there is more than one oncogenic pesticide used on a particular crop. As a class, the fungicides present special difficulties because nine oncogenic compounds account for about 90 percent of all fungicide sales. Further, these nine compounds present comparable risks and generally are viable substitutes for one another. In this situation the agency's historical approach—regulating one pesticide at a time across all of its uses—is not well suited to ensuring real risk reductions. This approach could even *increase* oncogenic risk when revocation of one agent allows a more potent oncogen to gain wider use.

The recommended strategy would also help preserve the benefits of pesticide uses that pose very low, but possibly not zero, risks. For example, most suspect oncogenic pesticides used on corn, soybeans, and cotton present very low dietary oncogenic risks. Further, the committee's analysis indicates that when estimated dietary oncogenic risks from herbicides or insecticides on these crops are deemed high, they can generally be substantially reduced through actions affecting one or two compounds. Most pesticides used on these crops would probably be passed over if a policy were in effect that targeted pesticide uses presenting relatively high dietary oncogenic risk. Such pesticide uses could come under scrutiny for other reasons, however, such as other health effects, ecological problems, or groundwater contamination.

The Adoption of an Analytical Framework

The EPA should develop improved tools and methods to more systematically estimate the overall impact of prospective regulatory actions on health, the environment, and food production. Rapid advances in computer technology, as well as the EPA's successful efforts to computerize major data sets like the Tolerance Assessment System (TAS) make such progress readily attainable.

The EPA's current approach to pesticide regulation focuses on the risks and benefits of one active ingredient at a time across all its uses. Much of the committee's analysis rested on new analytical manipulations of EPA data sets. Insights gained on the distribution and relative magnitude of risks and benefits associated with pesticide use are the foundation of the committee's recommendations. The analytical framework and data base that the committee developed on a prototype basis are described in detail in Chapters 3–5 and Appendix B. The framework the EPA might develop and utilize could be more thorough and precise. The committee's preliminary work provided intriguing new insights, however. The data base that the committee developed is extremely valuable in comparing the effectiveness of different regulatory policies that reduce dietary oncogenic risks from pesticides.

Use of new analytical tools and data bases could help the EPA get ahead of its growing work load. The refinement of such a system would allow the EPA to project with increased confidence a wide range of impacts associated with its regulatory actions. For example, the committee's rudimentary analysis demonstrates that certain strategies for implementing the Delaney Clause could increase dietary risk, and vigorous application of the Delaney Clause to tolerances for residues in processed foods may not be the most effective strategy for minimizing dietary exposure to oncogenic pesticides.

It is important to note that this study's preoccupation with oncogenic hazards simplifies the challenges that the EPA actually faces. In developing regulatory decisions, the EPA must take into account trade-offs between oncogenic risks and other sorts of health and environmental hazards among all pesticides registered for a particular use. Nonetheless, this more complicated task would be aided by the analytical tools discussed in this report.

NATIONAL RESEARCH COUNCIL
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February 27, 1989

Committee on Pesticides in the Diets of Infants and Children

At the request of the Congress and with the support of the U.S. Environmental Protection Agency, the National Academy of Sciences initiated a study in 1988 to examine risk assessment methods for pesticides in the diet, focusing on infants and children. To conduct the study, the Academy created the Committee on Risk Assessment Methods for Pesticides in the Diets of Infants and Children. This committee is established jointly under the Commission on Life Sciences, Board on Environmental Studies and Toxicology, and the Board on Agriculture.

The study will evaluate current risk assessment methods, and their use of average lifetime exposure estimates, in light of the potential sensitivities and increased exposure of infants and children. The exposure and potential sensitivity of infants and children to pesticides and other toxic chemicals has been the subject of scientific examination for several decades.

This study derives from the general consensus in the scientific community that new methods may be available to improve risk assessment methods and better protect the public health. It is important to note, however, that this study does not arise from the documented increase in any disease or adverse health condition in infants, children, or adults resulting from exposure to legal levels of pesticides in the diet.

The committee has only begun to study this issue. It plans to thoroughly examine each step of the risk assessment process, focusing on the scientific assumptions currently used. Critical review will be made of food consumption survey methods, pesticide residue detection methods and sampling procedures, and available information on the actual levels of pesticides to which infants and children are exposed. The usefulness of animal testing and extrapolation models, sensitivities of children to toxic substances, and the ultimate effect of these factors on methods used to project lifetime risk will also be examined. The committee will look for improvements in the risk assessment process that will (1) better protect infants and children from effects that may occur in childhood and (2) better protect children from effects that may occur later in life as a result of childhood exposures to pesticides in the diet.

A report on pesticides in the diets of infants and children was released earlier this week by the Natural Resources Defense Council. The committee will analyze this report and other pertinent documents as a part of its examination of the issues.

The committee's report is scheduled for completion in the fall of 1990. A list of committee members and staff is attached.

The National Research Council is the principal operating agency of the National Academy of Sciences and the National Academy of Engineering to serve government and other organizations. The Board on Environmental Studies and Toxicology is responsible to the National Research Council through the Commission on Life Sciences and the Commission on Physical Sciences, Mathematics, and Resources.

RESPONSES OF CHARLES M. BENBROOK TO QUESTIONS ASKED BY SENATOR KENNEDY

1. "It is imperative that good science be the foundation of regulatory decision-making. In testimony that has been given before this Committee, it is my understanding that the science of risk assessment is a discipline with several unknowns. When we talk about assuring the public that consuming foods treated with chemicals will not present more than a negligible risk of harm, what does that mean and how good is that assurance?"

   A risk is termed "negligible" when there is credible evidence available to judge that the risk is so small (generally, less than one-in-one million) and so unlikely to occur (at least a 95 per cent chance that the risk is less than one-in-one million) that it is the "functional equivalent of zero."

   Over the last decade the Food and Drug Administration has used quantitative risk assessment techniques to determine whether a potential risk exceeds a negligible level, the point at which appropriate regulatory actions are then taken under the general food safety clause of the Food, Drug, and Cosmetic Act. A principle recommendation of the 1987 NAS report "Regulatory Pesticides in Food: The Delaney Paradox" called for EPA to apply a similar negligible risk standard in setting pesticide tolerance levels. If such a standard were consistently applied in setting or adjusting tolerances, the committee concluded that the vast majority of the current potential dietary risk in the food supply would be eliminated, and that the remaining risk would be so small that it would almost certainly pose no real risk to consumers. In a word, it would be "negligible."

   It is important to note, however, that the public has reason to question whether some current pesticide uses pose a greater than negligible risk. Indeed, the Agency acknowledges that several hundred pesticide uses pose risks well above a negligible level, if residues are present on or in foods at current tolerance levels. Such levels would be legal, yet are clearly above what the EPA--or any government agency--would consider acceptable. Whether these uses of pesticides are actually causing cancer, birth defects, and other diseases, cannot be proven or disproven conclusively at the present time. By lowering exposure to these chemicals, however, risks can be lowered to negligible levels.

   As more complete toxicological data is generated and more prudent exposure estimates are made by EPA, the EPA should act quickly to utilize this improved information in adjusting tolerances downward when needed so that risks--even to the most susceptible population subgroup--are surely no more than negligible. Then the public can place greater confidence that all reasonable and prudent steps have been taken to protect public health from potential dietary risks from pesticides.

It is also important to recognize that there are a number of uncertainties in the risk assessment process which are rarely totally eliminated. When regulatory scientists reach a judgement that a chemical poses no more than a negligible risk, two key factors are taken into account.

First, an estimate is made of exposure to the chemical. In general, it is possible for regulatory scientists to develop reasonably accurate exposure assessments, particularly for chemicals that pose no unique difficulties for analytical chemists. An important, common problem, however, arises from the great diversity in potential exposure profiles for individuals across the population.

In developing exposure estimates resulting from a registered use of a pesticide, it is important to consider, among other factors, regional patterns of food distribution, whether the crop is processed or consumed fresh, how much of the crop is sprayed, at what rates and with what methods, and how often. In estimating exposure for individuals and certain key population sub-groups, like infants, other unique characteristics must be taken into account: the high rate of consumption of relatively few foods by children (in relation to body weight); dietary patterns that often include large portions of a few favored foods; ethnic food consumption patterns; where foods consumed are grown; food preparation and cooking habits; etc.

Until recently, the EPA has calculated "average" dietary exposure estimates for pesticides based on the assumption that each person is average in size, and consumes very small portions of some 350 distinct foods each day. Also, EPA still assumes that residues of pesticides that are likely to occur in food are distributed evenly throughout the national food supply. This assumption ignores the fact that many seasonal fruits and vegetables are grown, sprayed, and consumed in certain regions of the country, and hence consumers in that region will be exposed to residues reflecting regional pesticide use patterns, not national average use patterns. Meat and milk consumption patterns are also clearly not random across the nation.

The EPA is exploring new ways to more accurately and realistically estimate exposure by population subgroup. The goal is to develop dietary exposure estimates for the most "at risk" group of the population. High exposure population subgroups may receive as much as 100 times the residue that EPA currently estimates using "average" food consumption data. When regulations are based on protecting this group, the public can rest assured that a regulatory action posing no more than a negligible risk truly protects public health, indeed overprotects the majority of the population. Despite complexities in estimating exposure, the scientific tools are now available to eliminate much of the uncertainty in this process.

The second step in the risk assessment process must consider the toxic potential of the chemical. Estimating human toxicity from toxicological data derived in animal studies also involves many uncertainties. As a result, the standard methods used by government agencies include conservative assumptions designed to minimize the chance of substantially underestimating risk. Even with these assumptions, recent progress in toxicity testing suggests that certain pesticides may pose significant risks at levels of exposure once regarded as of no practical concern. (For example, data from the California Department of Health and the U.S. EPA suggest that routine food residues of the pesticide aldicarb may be far more toxic to infants and sensitive individuals than previously thought.)

While uncertainties abound in risk assessment, they can be lessened somewhat through a number of other scientific assessments involving new kinds of toxicity tests and epidemiological analysis of real world events. Much progress is underway in developing new sorts of disease markers, which will in turn help clarify whether pesticide exposure is or is not a cause of disease.

2. "In making decisions about which chemicals are to be permitted in the market place, benefits in formulation has traditionally been an important parameter to consider. In most cases the decision to use or not use a pesticide is not so clear cut. For example, risk calculations, which have

several scientific unknowns may indicate that a chemical is just over the negligible risk line. This chemical could be essential to a crop. How much variance should we include around the negligible risk value?"

> Most pesticides regulated by EPA have at least 5 and often 20 or more major food uses. Some chemicals have 50 or more minor crop uses. A review of recent EPA actions suggests that an assessment of benefits plays a role in determining the regulatory fate of relatively few uses--those that pose more than negligible risks, but are of unique value to producers in at least some regions.
>
> The 1987 NAS report "Regulating Pesticides in Food: The Delaney Paradox" contemplated a regulatory system in which benefits would play a limited role in certain cases.
>
> > *Benefits would generally not play a role when risks are less than a negligible level--registrations should be granted or retained without regard to benefits.
> >
> > *When risks are clearly well-above negligible levels, no amount of benefits would justify continued use of a pesticide--registrations would be denied or suspended.
>
> The committee that authored our 1987 report recognized that circumstances will inevitably arise when benefits should be taken into account in the regulatory process. But this was not a major point of the committee's deliberations, and no conclusions were reached on the role of benefits, nor how benefits should be defined and estimated. The committee also did not resolve the difficult question of how a regulatory agency should weigh an estimate of human health risks, measured as additional cases of some disease, against pesticide benefits expressed as additional dollar profits to farmers, or gains to consumers in the form of lower food costs.
>
> The role of benefits, and their definition in pesticide regulation is surely one of the most challenging policy and analytical challenges facing the Congress and EPA. I hope the committee will return to this issue for a more in-depth discussion since a consensus is growing that change is needed in how, and when, benefits are considered, yet there has been inadequate reflection, and virtually no solid analysis, of alternative ways to take benefits into account in the regulatory process.

RESPONSE TO FOLLOW-UP QUESTIONS
FROM EDWARD M. KENNEDY

1) *S. 722 would establish a requirement that within four years of enactment, the combined risk from all uses of a pesticide must meet the negligible risk standard. The National Academy of Sciences committee recommended that all pesticide residues on a single crop must meet the negligible risk standard. Could you provide us with more detail on the pros and cons of the two approaches?*

The report, Regulating Pesticides in Food: The Delaney Paradox, made two findings that appear to form the basis of language found in S. 722. The first and most important is that a consistently applied regulatory risk standard of one-in-one-million additional cancers over the lifetime of a population would reduce dietary cancer risk from pesticides by 98 percent and eliminate only 32 percent of all tolerances. (Consistently applied means that it would be applied evenly to both old and new pesticides, and to the sum of residues in raw and processed foods from each registered crop use of a pesticide.) This finding is particularly striking in contrast to the level of risk reduction expected following strict application of the Delaney clause, which would apply a zero risk standard to only a part of the food supply--and thus achieve significantly less risk reduction (about 45 percent less). The second relevant finding is that in certain cases a cropwide approach to risk reduction would more effectively reduce risk than EPA's current procedure of regulating the sum total of a pesticide's dietary risk one pesticide at a time. This is particularly true in the case of fungicides since 8 major pesticides pose oncogenic risks of roughly comparable magnitude, and these pesticides are often substitutes for one another.

It is important to note that the 98 percent risk reduction achieved under the committee's theoretical analysis required that all pesticide tolerances on a crop that exceeded the one-in-one-million risk standard were automatically revoked. S. 722 does not require this automatic revocation of tolerances that present greater than one-in-one-million risk but rather allows tolerances to be lowered to meet the risk standard. This is a key difference between S. 722 and the policy scenario the committee studied. By lowering tolerances rather than eliminating tolerances, the risk reduction achieved under S. 722 will be somewhat less that the 98 percent achieved under the committee's analysis. Still, the degree of risk reduction would clearly be sizable, possibly approaching 85 to 90 percent.

Strengths of Cropwide Regulation

In contrast to current EPA risk assessment procedures and standards that assess all uses of one pesticide, the principal argument for a cropwide regulatory approach is to avoid increasing risk by canceling a pesticide that proves to actually be less hazardous than other pesticides, but which is restricted or cancelled purely because EPA had complete data on it before other pesticides, or scheduled its data reviews earlier. This scenario is most likely to occur for fungicides; about 8 fungicides of roughly equivalent toxicity account for about 90 percent of all fungicide use and a majority of all dietary cancer risk from pesticides. Similar but not so serious problems could also arise in the corn-soybean herbicide area.

Regulatory actions that paradoxically increase risk are most likely when pesticides are regulated one at a time. For example, it is very complicated to ensure net risk reduction following decisions on captan in 1989, benomyl in 1990, and the EBDC's in 1991. In contrast, under S. 722 all pesticides will meet a one-in-one-million risk standard at the same time. The problem of increasing risk through wider use of more hazardous pesticides following regulatory actions would thus be largely eliminated.

An additional strength of cropwide regulation is that it more effectively meets the needs of growers. In fact, agricultural needs for certain groups of pesticides are so compelling that, even though S. 722 does not formally require cropwide regulation until six years after passage, cropwide analyses will begin at the four-year stage. This is because effective implementation of the four-year phase of S. 722 (risk reduction across all uses of a single pesticide to a combined negligible risk level) will require EPA to analyze growers' needs and the effectiveness of each pesticide on each crop in order to determine, for each pesticide, which tolerances to keep, which to lower and by how much, and which to revoke. Thus, one could argue for amending the bill to require cropwide regulation at the four-year stage to avoid confusion in implementation.

Strengths of a Chemical Approach to Regulation

An important advantage of the chemical-wide approach (regulating based on total exposure and estimated risk from all registered uses of one pesticide) is that it is consistent with and, in many ways, identical to current EPA practice. EPA currently regulates dietary exposure to a pesticide by adding up the risks from all of its food uses to determine if the risks outweigh the benefits. The important differences between S. 722 and current EPA practice are that S. 722 requires that all pesticides meet a prescribed risk standard at the same time, and that the risks from all uses of a pesticide have not less than a 100-fold margin of safety or cause no more than a one-in-one-million additional cancer risk over the lifetime of the exposed population. Historic EPA policy and procedure is different from S. 722 principally because it allows a pesticide's summed cancer risks to be greater than one-in-one-million when justified by benefits.

It is noteworthy, however, that in the October 19, 1988 Federal Register EPA proposed to adopt procedures based on the recommendations of the committee that would, in the agency's view, apply a one-in-one-million risk standard to dietary risks from pesticides, except in cases when extraordinary benefits were present. While some would argue with the methods EPA apparently intends to use in implementing this policy, it is important to note that EPA is on record in favor of a negligible risk standard, despite its opposition to this bill.

In Sum

The conclusion in Regulating Pesticides in Food: The Delaney Paradox supporting a cropwide approach to pesticide regulation is proposed as an alternative to current EPA practice of regulating pesticides one at a time. The report points out cases in which this alternative approach is particularly necessary to avoid regulatory decisions that paradoxically increase risks. Because S. 722 would require that all pesticides meet a negligible risk standard at the same time, it is unlikely under S. 722 that risk could markedly increase as farmers switch to riskier pesticides. Nonetheless, a principal advantage of cropwide risk reduction remains. That is, it is more suited to the needs of agricultural producers and researchers in developing alternative pest control practices consistent with risk reduction strategies and producer needs.

In contrast, a chemical approach to risk reduction is more suited to and is, in many ways, nearly identical to current regulatory programs and policies. However, bringing all pesticides in line with one standard simultaneously will likely change chemical regulation into cropwide risk management out of practical need.

2) *In addition S. 722 would revise the way EPA sets tolerances on pesticide residues. EPA could only assess risks from particular pesticides, as opposed to their current risk-benefit determination. What is your opinion of only assessing the risk of adverse health effects in considering tolerances for pesticide residues?*

The committee made no specific recommendations or evaluation of the benefits assessment process for pesticides at EPA. They did note, however, that benefits would likely need to be considered when risk reductions of this magnitude were attempted. The nature of an appropriate benefits assessment process was not specified, however, nor was EPA's current method of assessing benefits endorsed as appropriate.

My opinion--and that echoed by the Administration witnesses at the hearing--is that pesticides, like other chemicals added to food, should meet basic public health standards applied to the food supply. The two standards most commonly applied to food are a one-in-one-million additional cancer risk standard for oncogens, and a 100-fold margin of safety for non-cancer risks. S. 722 contains these standards. To some, it is noteworthy and objectionable that the one-in-one-million cancer risk standard in S. 722 weakens current law applicable to concentrating residues of pesticides found to cause cancer in humans or animals in processed foods. These residues are currently regulated as food additives and are thus presumably prohibited by the Delaney clause. A principal justification for allowing a negligible increase in allowable levels of exposure to residues of cancer causing pesticides in food, as called for in S. 722, is the general recognition that pesticides confer distinct benefits to food production that other food additives do not, and that consistent adherence to a negligible risk standard can very efficiently eliminate most of the potential risk from pesticides in the diet. (Another pivotal justification for negligible risk is that a consistently applied negligible risk standard would achieve greater risk reduction than the Delaney clause's zero risk standard applied only to processed food.)

Nonetheless, for certain foods grown in some areas, production costs may increase and production levels may fall under the four- and six-year implementation phases of S. 722. In certain cases, therefore, the consumer benefits of a somewhat less strict standard may need to be weighed in light of any significant and well-documented disruptions in food supply that may result from S. 722. It is essential, however, that the agency (and probably law) more clearly and explicitly define what benefits are to be taken into account, and how they are to be measured. Benefits are now measured in terms of the cost of alternative pesticides and any yield or quality losses. Benefits are not currently expressed in terms of their effects on those who bear the risk (food consumers). A critical policy issue at the heart of the benefits debate is whether the food consuming public should be asked to bear greater than negligible risks if they do not receive direct benefits in the form of a more nutritious and affordable food supply.

3) *You indicate that establishment of a one-in-a-million negligible risk standard would eliminate the vast majority of dangerous pesticides, and only 32 percent of all the tolerances covering cancer-causing pesticides would need to be revoked. The food industry argues that revoking pesticides under this standard would be disruptive to agriculture. To your knowledge, are their [sic] safer pesticides that could be substituted, such that agriculture productivity would not be reduced?*

Under the committee's analysis, a one-in-one-million risk standard would revoke 32 percent of all tolerances for carcinogenic pesticides, thereby reducing dietary cancer risk from pesticides by 98 percent. Unlike S. 722, however, the committee's analysis required that all pesticide tolerances on a crop that exceeded the one-in-one-million risk standard were automatically revoked. S. 722 does not require this automatic revocation of tolerances that present greater than one-in-one-million risk but rather allows tolerances to be lowered to meet the risk standard. This flexibility to lower tolerances to acceptable levels is an important attribute of S. 722, and would accord producers and the agrichemical industry an opportunity to develop modified formulations and use patterns for many products that would bring risks down below a negligible level.

It is difficult to predict what percent of current tolerances might be lost under S. 722. It is certain, however, that the claim cited above is unfounded, and exaggerates the impact of S. 722. It is also important to acknowledge that under current EPA policy and the ongoing re-registration process (and without S. 722) a large number of the riskiest pesticide uses will be abandoned by registrants and cancelled by EPA. Based on recent agency experience, perhaps 15 to 20 percent of the riskiest uses are likely to be cancelled as a result of the data generation costs required to gain re-registration. To meet the two-year risk reduction goals of S. 722, at most another 5 to 10 percent of published tolerances may need to be revoked. Others will be adjusted downwards but not require major changes in current use patterns.

In contrast to exaggerated claims of the impact of S. 722, what appears to be true is that for many major commodities (corn, cotton, wheat, soybeans, barley, and rice) few or no revocations in tolerances for any pesticides used on these crops would be necessary. In fact, there are no data to support the claim that under S. 722 any tolerances for widely used pesticides would have to be revoked for any of the major field crops listed above. Tolerances may have to be reduced for two or three important compounds, but this appears feasible since tolerances are currently set well above actual residue levels, a point repeatedly made during the hearing.

Tolerance reduction, as an alternative to revocation, is a feasible and effective means to reduce risk on the above crops because the majority of the dietary risk for these crops is derived from residues of fungicides used to protect seeds and pre-plant herbicides. Most of this risk as currently measured is theoretical, actual risk is far lower. Tolerances for these uses could easily be reduced without affecting the use or availability of nearly all compounds. In addition, for many major field crops farmers have numerous non-pesticide control alternatives to control certain insects, diseases, and many weeds in these crops, or technologic and agronomic systems which markedly increase the efficiency of pesticide use so that an adequate degree of control is attained with much less pesticide.

The situation with fresh fruit and vegetable production in some regions is more problematic. Nonetheless, the claim that S. 722 would result in a 32 percent reduction in available uses and tolerances is an inaccurate application of the committee's findings to S. 722. While some important pesticides used on a few crops in certain regions may not meet the negligible risk standards even when tolerances are reduced to their lowest effective level, the ability of farmers to develop alternative control strategies has always been underestimated by EPA in assessing the potential loss of benefits when a pesticide is cancelled. Necessity is the mother of invention on the farm, and biotechnology, bio-control, integrated pest management (IPM), and safer pesticide alternatives to reduce risk are available or within reach. More aggressive regulatory policies--as envisioned in S. 722--will clearly increase the importance of a timely, strategic response by federal and state agricultural research and education institutions to producers' needs for effective alternative control options. Congressman George E. Brown has, in recent months, aggressively pushed the USDA to play a more proactive role in accelerating and targeting research and development efforts. I hope this committee will also lend its support to this effort as it continues to work toward passage of S. 722.

The CHAIRMAN. Mr. Roe.

Mr. ROE. Thank you, Mr. Chairman. I am David Roe from the Environmental Defense Fund. I have three main points.

The first is that this legislation is an important marker because it acknowledges that the present system of pesticide regulation is a failure. You have heard plenty of evidence. I will add only that when my organization looked at existing tolerances compared to the 10-6 level, we found that they varied upwards from that by a factor as much as 45,000 times as much risk allowable under tolerance, compared to 10-6. That is in the cases where the numbers are not in controversy.

Mr. Kimm said we will find more ALARs. I agree with him. I do not understand why he takes any comfort in that statement.

Cost/benefit analysis is the screen behind which much of this failure has taken place, and I think its day is waning. I see as very good news the fact that EPA recently conceded that there needs to be health-based limits on pesticides in food, a health-based ceiling no matter what the benefits are. In other words, no risk/benefit calculation should ever exceed a fixed level. That I think is something this committee can build on that is very consistent with this bill. The notion of bright lines separating acceptable from unacceptable and consistent lines is the key.

The second point I have to make is that the source of this failure is deeply built into the structure of present law. If you look at the incentives in the law, the real world incentives offer delay, confusion, and ad-hoc adjustment of scientific decisions on a case-by-case basis over as much time as possible. EPA and FDA have basically been given the task of trying to push a puddle of water uphill. Well, it is physically do-able if you have got a good enough squeegee, but it is very hard to do. And any little flaw in the process, and the whole things leaks away from you.

The regulatory failure that has been on the front page of the Washington Post this week—under the Clean Air Act, for example, being able to regulate only seven toxic chemicals out of 329 in most of two decades—that is why it is a structural defect. And that is not going to change unless the structural incentives in the law are shifted.

My third point is that this incentive shift has already been accomplished in the statute that has already been in effect for over a year in California with extremely productive results. So this is not unprecedented. This is not simply a theoretical improvement. There is a model for it. The name of the statute, as you know, is Proposition 65. Some members of the committee are quite familiar with it. I describe it in my testimony. Let me just indicate to you what it has accomplished in less than a year of being in effect.

There are uniform health-based standards for chemicals that cause cancer or birth defects across the entire spectrum of places people are exposed to them—whether they are exposed to them in food, air, water, what have you. There are clear quantified numerical limits that have been set on 45 chemicals in 18 months. Compare that to seven by EPA in 18 years. There are 150 pages of regulations prescribing methodology, exposure, the nuts and bolts that have taken EPA and FDA so much time that you heard re-argued here this morning, and not one word of those regulations—not one of those numbers—has been challenged in court by any industry.

There was talk about being on the cutting edge of science. It appears that we have been using the back end of the knife. And if you turn the knife over and use the sharp edge, you can get a great deal done. By Federal standards, this progress is extraordinary. It has gotten lead out of cans; it has gotten new aflatoxin techniques, new aflatoxin control techniques in peanut butter, all automatically and all based on the shift in incentives.

Senator HATCH. [Presiding.] Keep going. We are listening.

Mr. ROE. Yes. The last point I have to make, this is really quite important because there is a fundamental fallacy in much of the testimony you heard this morning, which is that to get improvement Government must do all the work. Therefore, you heard about $50 million for testing the pesticides on apples. You heard about doubling the workload of EPA. There is another way to do it. The Proposition 65 approach puts the burden of proof in specified cases on industry, and industry brings forward the data rather than having to build up the bureaucracy to produce it.

The only other point that I want to make is that it is essential in this bill that there not be pre-emption. It is not in here now, but this must be said because the food industry has made pre-emption in this area their absolute top priority, even after having their arguments disproven in the Reagan White House, so much so that the Bush Administration has had to take special steps to instruct its agencies not to continue entertaining pre-emption talk. It is too bad that that needs to be said, but it is very important from our point of view that it be clear to the committee that no pre-emption is an absolutely crucial element of any bill in this area.

Thank you very much.

[The prepared statement of Mr. Roe along with responses to questions asked by Senator Kennedy follows:]

PREPARED STATEMENT OF DAVID ROE

Mr. Chairman and members of the Committee:

Thank you for this opportunity to testify on S. 722, The Food Safety Amendments of 1989. I am David Roe, senior attorney with the Environmental Defense Fund, located in EDF's West Coast office.

EDF is a national not-for-profit organization of over 100,000 members with a staff of scientists, economists, lawyers and other professionals dedicated to protection and enhancement of public health and the environment, and to the conservation and rational use of natural resources. EDF was founded over 20 years ago out of concern over the effects of pesticides, was instrumental in the original ban of DDT and several other pesticides, and has maintained a major focus on toxic chemicals including pesticides throughout its existence.

My testimony this morning offers three main points:

1. This bill marks a recognition that an entire era of pesticide regulation has failed; and that the public's expectation of a guaranteed-safe food supply, particularly where cancer-causing pesticides are involved, is being routinely violated.

2. The causes of this failure are embedded in the very structure of the law, and are not merely the fault of timid, overworked, or industry-sympathetic regulators. Unless basic structural incentives are changed, improvements will be marginal and slow.

3. Structural incentives have already been successfully shifted in a toxic-control statute that has been in effect in California for over a year, with extremely productive results.

Issues of preemption, risk assessment methodology, threshold-effect standards, GRAS, etc. are then treated in separate paragraphs.

1. THE FAILURE OF SAFETY GUARANTEES

Recent events and the testimony of other witnesses this morning make this point with considerable force. The Delaney Clause flatly promises that cancer-causing chemicals, including pesticides, will not be added to people's food. And both industry and government have been quick to point to Delaney when trying to reassure the public. The National Academy of Sciences study reveals the emptiness of the promise.[1]

EPA also claims to regulate cancer-causing pesticides in general at the one-in-a-million (10^{-6}) level.[2] So does FDA.[3] However, EDF research has shown that government-set tolerances for human intake of pesticides now known to cause cancer allowed risks many times higher--as much as 45,000 times higher--for chemicals where the calculation of the relevant numbers is not in doubt. See Attachment A.

Even the erratic and inconsistent application of existing standards is not the full story. In many cases, data are simply lacking, either about the health effects of the pesticide itself, or about the extent to which people are actually being exposed to it.[4] Public assurance is being provided by the ostrich method: you can't see any danger if your head is in the sand. Unfortunately, ignorance is not bliss when it comes to toxic chemicals like pesticides--at least, not for the public being exposed.

Emerging Consensus on Health-Based Standard

"Cost-benefit analysis" has been th[illegible] rationale for the grossly inconsistent application of human h[illegible] standards to different pesticides in different crops. Und[illegible] pressure of recent controversy, however, EPA has acknowledged (f[illegible]at we believe is the first time) that it should observe a health-based ceiling for carcinogenic pesticide risk, i.e., that no matter what the benefit, risk should not be allowed to exceed a fixed level[5] (identified by EPA's top pesticide official as 10^{-5}). This Committee should not underestimate the importance of this policy statement: once the concept of a health-based ceiling on risk is established, there appears to be a relatively narrow band of controversy over where it should be set. (EDF strongly supports the 10^{-6} level contained in S. 722 as the no-exceptions ceiling; see also comments on methodology below.)

2. STRUCTURAL CAUSES AND STRUCTURAL REFORMS

The unsatisfactory results of the existing federal pesticide regulatory system can be loosely summed up as delay, confusion and inconsistency. It is critical that the Congress recognize the extent to which these results are foreordained, by a statutory structure that rewards delay and reinforces the tendency to debate technical and semi-technical issues *ad infinitum*.

In effect, the burden of proof to establish key elements of any violation of the present law is on the government--not only the presence of a dangerous pesticide residue in food, but also the definitions and technical criteria by which "danger" or "violation" is to be gauged. Since the law is not enforced until (and unless) these technical issues are settled and the results prescribed in regulation, regulated industries have a wholly understandable incentive. This incentive is independent of their degree of good faith or concern for human health, and to recognize it implies no necessary criticism of any individual company; the incentive is built into the structure of the regulatory system. Thus, it should come as no surprise to see the relevant actors engaging in as much techical debate as possible, for as long as ossible, or to notice that the few results (when they finally emerge) are *ad hoc* rather than generic, so that the same technical issues can be reargued again and again in each specific case. In this context, even EPA's recent indication that maximum health risks should be consistent from one carcinogenic pesticide to another is a radical step. (This principle is, of course, one of the most important reforms contained in S. 722.)

The Need for Incentive-Conscious Structural Reform

Closing loopholes and tightening the screws on the existing system will bring important incremental improvements, for example in the control of so-called inert ingredients, but will not by itself eliminate built-in disincentives to progress. Until it becomes in industry's (and regulators') genuine self-interest to reach timely closure on quantitative technical issues, EPA will continue to labor slowly uphill on a chemical-by-chemical basis, and the familiar pattern of delay, confusion, and *ad hoc* accommodation is likely to repeat itself.

But can such a structural incentive shift be accomplished through legislation? It may sound attractive in theory, but seem unreachable in practice.

However, just such a shift has been incorporated into the law on toxic chemical controls in the State of California, where it has been in effect for more than a year and where it has produced some startlingly successful results.

3. EXPERIENCE TO DATE WITH INCENTIVE-CONSCIOUS TOXICS CONTROLS

Proposition 65, California's Safe Drinking Water and Toxic Enforcement Act of 1986, was enacted by direct ballot initiative in November 1986, by approximately a 2:1 voting margin, and its key provisions began going into effect in February 1988. See California *Health and Safety Code* Sec. 25249.5 *et seq.* As a new approach to the control of toxic chemicals, it has been the focus of considerable controversy and industry attack over the last two years, particularly from the national food and drug industry.

However, a White House working group formed to investigate Proposition 65 by then-Attorney General Edwin Meese under the auspices of the Domestic Policy Council, in response to industry pressure, concluded after several months of work that industry complaints about the law were "vastly overstated" and "unrealistic," and that the law's likeliest impact on food and other consumer product producers would be "of the nature of additional quality control expenditures," i.e., keeping their products within compliance with Prop. 65 exposure limits.[6] (The working group, chaired by Dr. Thomas Moore of the Council of Economic Advisers, was careful to state its assumption that California would not adopt "highly stringent exposure standards for any widely used pesticides."[7] Since the group's report was issued, California has not changed the standard applicable at the time the report was written.)

The basics of Proposition 65, as they relate to direct human exposure to toxic chemicals (e.g., in foods), are straightforward. The Governor in consultation with experts is charged with identifying chemicals that are "known to the State to cause cancer or reproductive toxicity." Some 280 have been listed to date. Then, one year after listing, it becomes illegal to expose anyone to the listed chemical without warning, unless the exposure is provably below a *de minimis* level. Although warning is the only requirement under this part of the law, it is intended to provide a strong incentive for producers to reduce toxic exposures, rather than to have to give cancer and/or birth defect warnings to their customers. And so far it appears to be working very much as intended, despite dire predictions.[8]

The Shift in Incentives

For this Committee's purposes, the most relevant provision of Proposition 65 is the way in which the *de minimis* concept is applied.
De minimis exposures escape the coverage of the law, in very much the same way as contemplated under S. 722. However, Prop. 65 contains one key structural innovation. The burden of proof in establishing that an exposure falls within *de minimis* levels falls on the defendant, i.e., the entity responsible for the exposure.

This simple-sounding shift has had profound consequences. Instead of waiting for government to prove that a given exposure is "above the line," regulated industry has faced the need of showing that the same situation is "below the line"--and suddenly has been eager for regulations that define and quantify those lines. Continued ambiguity about "how much is too much" of a particular chemical is no longer in industry's self-interest; instead, it creates worrisome legal risks. For the first time, therefore, the community of regulated industry has had a strong incentive to help the California regulatory agency succeed in defining and quantifying those levels, for every specific chemical of concern.

Success to Date

In the presence of this new incentive, California managed to draw clear quantity-specific exposure limits for more chemicals in the first twelve months of the Prop. 65 era than EPA has managed to accomplish in the previous twelve years, under any or all of the federal laws applying to control of toxic chemical exposures (e.g., Clean Air Act, Safe Drinking Water Act, Toxic Substances Control Act). In fact, much of the scientific information on which the California limits were based came directly from the file cabinets of EPA, which had long since completed reviews of the relevant research. The difference was that, for once, there was a premium on getting to the bottom line.[9] There are now specific enforceable limits for 45 specific toxic chemicals[10] (compared to 8 under almost twenty years of the Clean Air Act), with more in the pipeline, and a standing invitation to industry to nominate any other chemicals of individual concern for accelerated attention.

Driven by the same incentives, California regulators have also managed to enact over 150 pages of detailed regulations, specifying not only risk standards but also risk assessment methodology, exposure assumptions and calculating methods, etc., to be applied uniformly to all chemicals covered by the act--in short, the nuts and bolts of the risk assessment/risk management enterprise.[10] And not one word or number of those regulations has been challenged in court by any regulated industry, despite having been highly controversial during the drafting process, and despite having been in actual and enforcealbe effect for more than a year. This, by the standards of EPA, is a revolutionary rate of progress.

Implications for Federal Pesticide Tolerance-Setting

It seems likely that use of Prop. 65-type mechanisms could greatly accelerate EPA progress in setting clear, uniform, and scientifically consistent tolerance levels. The same mechanisms could also be used to enlist industry cooperation in meeting firm deadlines and producing much clearer and more final regulatory definitions than have been customary to date.

At a minimum, ED [illegible] ds that pesticides known to be carcinogenic and/or reproductively toxi [illegible] bject to a burden of proof on the pesticide user (or seller of the resulti [illegible] duct) that any exposures to such pesticides are below a defined level of "negligible risk," less than or equal to a tightly defined 10^{-6} level.

ADDITIONAL SPECIFIC COMMENTS

A. *Preemption*

EDF strongly emphasizes that any federal pesticide bill *must not preempt state law*. At this stage, given the undisputed record of the last decade, the federal government has forfeited any basis for claiming to the public that its efforts are sufficient to guarantee the absence of dangerous levels of toxic chemicals including pesticides in the nation's food supply. In recent years, ironically, industry has regularly sought preemption as a means of *weakening* protections in the handful of instances where states have exercised leadership in filling the gap. State efforts have taken place where the federal government has failed to act, for example in the case of California's 1977 ban on DBCP, ratified two years later by the federal DBCP ban once state action had made the issue unavoidable. Proposition 65 is a recent conspicuous example of industry effort to avoid effective controls, in that case through desperation lobbying even after industry claims and predictions were authoritatively rejected. (The Bush Administration has had t issue special anti-preemption instructions on Proposition 65 to its agencies to relieve them of relentless industry lobbying pressure in the last few months, repeating a massive pressure campaign in the closing days of the Reagan Administration.)

B. Risk Assessment Methodology

S. 722 is currently ambiguous, in an area where differing definitions can rfesult in widely varying degrees of exposure risk (even if all other factors are equal). EDF recommends the methodology specified in California regulation over two years ago, which remains unchallenged:

> The absence of a carcinogenic threshold dose should be assumed and no-threshold models shall be utilized. In the absence of other scientifically appropriate extrapolation models methods utilizing the linearized multistage model for extrapolation from high to low doses, with the upper 95 percent confidence limit of the linear term the most appropriate for expressing the upper bound of potency are preferred.

22 California Code of Regulations Sec. 12703(a)(5).
The same subsection also specifies other criteria for quantitative risk assessment. 22 CCR 12703(a).

EDF strongly supports the provisions of S. 722 covering "identifiable subgroups" and the filling of data gaps, as essential aspects of a system that can provide genuine and meaningful assurance to the public about pesticide risks in particular foods.

C. Inert Ingredients

EDF also strongly supports the treatment of so-called "inert ingredients" on the same footing as so-called "active" ingredients. This is a long overdue reform the need for which has been amply documented. A number of chemicals which are known to cause cancer, including benzene and vinyl chloride,[12] are permitted by present law to be in pesticides with essentially no controls and no controls on residues.

D. GRAS

S. 722 makes the mistake of assuming that chemicals classified in FDA regulation as "generally recognized as safe" (GRAS) are in fact safe. The Committees should be aware that GRAS is no guarantee of safety, and that indeed, at least one known carcinogen, acetaldehyde,[13] is on the current GRAS list.

E. Standard for Threshold Effects

S. 722 uses a safety factor of 100 times the NOEL, where the NOEL is derived from animal data. Although this may be adequate in some instances, it is not adequate as a general standard for chemicals that are known reproductive toxins. EPA itself regulates some reproductive toxins at a 100x level and others at a 1000x level.

The assumption of "adequate data" for generating a reliable NOEL from animal data is also one that deserves close scrutiny and cannot be taken for granted. It should not be incorporated into statute unless a definition of adequqte data is included.

FOOTNOTES

1. National Academy of Sciences, Board on Agriculture, *Regulating Pesticides in Food: The Delaney Paradox* 1987. See also *Public Citizen v. Young*, 831 F.2d 1108 (D.C. Cir. 1987).

2. Oral testimony of Jack Moore, Ph.D., Acting Deputy Administrator, EPA, on H.R. 1725, before the Subcommittee on Health and the Environment, U.S. HOuse of Representatives, May 17, 1989.

3. NAS, note 1 *supra*, at 94.

4. See, e.g., GAO, *Pesticides: EPA's Formidable Task to Assess and Regulate Their Risks. GAO/RCED-86-125. April 1986. p. 40.*

5. Jack Moore, note 2 supra.

6. Executive Office of the President, Council of Economic Advisers, *Economic Analysis of Proposition 65.* December 5, 1988, at 6-7.

7. *Id*. at 7.

8. See, e.g., Kizer *et al*., "Sound Science in the Implementation of Public Policy: A Case Report of California's Proposition 65," *Journal of the American Medical Association* vol 260, no. 7, August 19, 1988 [the authors are the chief regulatory officials in CAlifornia charged with implementation of Proposition 65]; Roberts, Leslie, "A Corrosive Fight Over California's Toxics Law," *Science* vol. 243, p. 306 (1989); Diringer, Elliot, "EPA Chief Backs California's Controversial Anti-Toxics Law," *San Francisco Chronicle* Oct. 4, 1988; Totten, Glenn, "*Special Analysis*: Controversial Proposition 65 Provokes Industry Outrage, 'Quiet Compliance' as it Marks Second Anniversary as Law," *Chemical Regulation Reporter* April 5, 1989, p. 5; Russell, Cristine, "California is Getting Tough on Toxics; Will its Controversial Environmental Law Become a Model for the Nation?" *Washington Post* Weekly Health Journal, May 23, 1989 [cover story].

9. "Sound Science," note 8 *supra*.

10. 22 Calif. Code of Regulations Div. 2, Chapter 3, Articles 7 & 8, Sec. 12700 *et seq*.

11. 22 CCR Div. 2, Chapter 3, Sec. 12000 *et seq*.

12. 22 CCR Sec. 12000.

13. *Id*.

ATTACHMENT A

[NOTE: all comparisons in Table I are between EPA allowable exposures and an exposure level of 10^{-5} (i.e., one-in-one hundred thousand). For comparison to an exposure level of 10^{-6}, all ratios reported in this study should be multiplied by 10.

[Thus, the allowable federal levels exceed the 10^{-6} level by a factor which varies from 100 to 45,000.]

COMPARISON OF PESTICIDE EXPOSURE LIMITATIONS FOR AGRICULTURAL PRODUCTS UNDER PROPOSITION 65 AND UNDER ENVIRONMENTAL PROTECTION AGENCY REGULATIONS

This is a study undertaken by Environmental Defense Fund staff to compare two sets of exposure limits for known carcinogenic pesticides on specific agricultural products: limits set by the Environmental Protection Agency (in the form of pesticide tolerances) and those identified in regulations under Proposition 65 as reflecting "no significant risk" at the 10^{-5} level. Tolerance levels are the maximum levels of pesticides that may legally remain in food under federal regulation.

Nine pesticides that appear on the Proposition 65 list as chemicals known to cause cancer have had numerical exposure limits set by state regulation, each at the level determined by the state to represent "no significant risk." (22 CCR 12711) (see Appendix A). Of those nine, the Environmental Protection Agency has set tolerance limits on specified raw agricultural food products for the following:

Heptachlor (at 40 CFR 180.104 and 180.319)
Ethylene Dibromide (at 40 CFR 180.126 and 180.397)
Toxaphene (at 40 CFR 180.138 and 180.319)
Ethylene Oxide (at 40 CFR 180.151)
(see Appendix B)

Federal as well as state limits are also available for two listed Proposition 65 carcinogens that are added directly to food products, the federal limits appearing in regulations of the Food and Drug Administration:

Vinyl Chloride (as coating on fresh citrus fruit)(at 21 CFR 172.210)
Benzene (in modified hop extract)(at 21 CFR 172.560)

Results

When maximum daily exposures are calculated for specific agricultural products at allowable federal (i.e., EPA tolerance) levels, results show that the exposures exceed the levels identified as "no significant risk" under Proposition 65 regulations by as much as 4500 times, and at minimum by a factor of 10. Results are shown in Table 1.

Method of Calculation

The EPA sets different tolerance levels for different categories of agricultural products within each category. One food product for each level of tolerance was selected. The average daily consumption of that food was then calculated from consumption figures taken from the Nationwide Food Consumption Survey's Continuing Survey of Food Intakes by Individuals, Human Nutrition Information Service, U.S. Department of Agriculture (see Table 1). Conversion from parts per million (ppm) to micrograms per day was calculated by multiplying the figure in parts per million by the average daily consumption (see Appendix C).

In some cases EPA tolerance levels are set for commodities such as "wheat," and consumption figures are not available for a "wheat" category. In this study, consumption of wheat and grains was calculated as consumption of bread, and consumption of crude soybean oil was calculated as consumption of total fats and oils.

April 10, 1989

Prepared by: Diane Fisher, Ph.D.
Susan G. Rose

TABLE I

PESTICIDE EXPOSURE LEVELS--

Comparison of Levels Allowed under Federal Law

With Levels Representing "No Significant Risk" under Proposition 65

[*compare* column V *with* column VI]

I	II	III	IV	V	VI
CHEMICAL	RAW AGRICULTURAL PRODUCT	EPA TOLERANCE LEVEL (ppm)	AVERAGE DAILY CONSUMPTION FOR ADULTS (grams/day)[1]	ALLOWABLE DAILY EXPOSURE (micrograms/day)[2]	PROP. 65 "NO SIGNIFICANT RISK" EXPOSURE LEVELS (micrograms/day)
Heptachlor	Lettuce*	0.1	40.72	4.07	0.2
Ethylene Dibromide	Potatoes*	75	188.46	14,134.5	3
	Sweet Corn*	50	111.29	5,564.5	3
	Pineapple	40	109.27	4,370.8	3
	Lettuce*	30	40.72	1,221.6	3
	Peanuts	25	57.95	1,448.7	3
	Asparagus*	10	Data not available		3
	Strawberries*	5	112.41	562.05	3
	Soybeans	125	209.38[3]	26,172.5	3
Toxaphene	Apples*	7	155.80	1,090.6	0.6
	Wheat*	5	65.48(as bread)	327.4	0.6
	Bananas*	0.3	105.77	31.73	0.6
	Soybeans	2	209.38[3]	418.76	0.6
	Sunflower seeds	0.1	Data not available		
	Crude Soybean oil	6	24.05 (as total fats/oils)	144.30	0.6
Ethylene Oxide	Walnuts*	50	50.01	2,500.5	2
Interim Tolerances					
Heptachlor	Peppers	0.1	Data not available		
	Tomatoes	0.02	97.83	1,956.0	0.2
	Berries* (not strawberries)	0.01	Data not available		
Toxaphene	Milk	0.05	326.20	16.31	0.6
Ethylene Dibromide	Soybeans	0.0001	209.38[3]	43.83	3
	Grains	0.9	65.47(as bread)	58.93	3

* For complete list of all agricultural products at this tolerance level see attached regulations

I	II	III	IV	V	VI
CHEMICAL	RAW AGRICULTURAL PRODUCT	FDA ALLOWABLE LEVELS	AVERAGE DAILY CONSUMPTION FOR ADULTS (grams/day)	ALLOWABLE DAILY EXPOSURE (micrograms/day)	PROP. 65 "NO SIGNIFICANT RISK" EXPOSURE LEVELS (micrograms/day)
Vinyl Choride	Fresh Citrus Fruit (as coating)	"As an aqueous dispersion containing a minimum of 75% water when applied"	Data not available	Data not available	0.3
Benzene	Modified Hop Extract	1ppm	Data not available	Data not available	20

Footnotes to Table 1

1. Daily consumption figures calculated from Foods Commonly Eaten by Individuals: Amount Per Day and Per Eating Occasion, Human Nutrition Information Service, U.S. Department of Agriculture, March 1982 and CSFII, Nationwide Food Consumption Survey Continuing Survey of Food Intakes by Individuals, Human Nutrition Information Service, U.S. Department of Agriculture, 1985-1986.

2. (Column III x Column IV = Column V). For explanation of calculations, see Appendix C.

3. Probable overestimate: Includes consumption of all canned beans.

APPENDIX A

Listed Proposition 65 Carcinogens Identified as Present in Food Products*

Aldrin

Arsenic

Benz(a)pyrene (B(a)P)

Benz(a)anthracene (B(a)A)

Benzene

Cadmium

Chlordane

Chromium 6

1,2,Dibromo-3-chloropropane (DBCP)

DDE, O, P; DDE P,P

DDT, O,P; DDT P,P

Dieldrin

Ethylene dibromide (EDB)

Ethylene oxide (EtO)

Heptachlor, Heptachlor epoxide

Hexachlorobenzene

Hexachlorocyclohexane (technical grade)--alpha & beta isomers (BHC, alpha BHC, beta)

Polychlorinated biphenyls (PCBs)

Toxaphene

Vinyl Chloride

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*Gunderson, FDA Total Diet Study, April 1982-April 1984: Dietary Intakes of Pesticides, Selected Elements and Other Chemicals, Data Tables (distributed separately by the Association of Official Analytical Chemists and covering the period, April 1982-April 1986)

APPENDIX B

EPA Tolerances

(excerpts from the Code of
Federal Regulations, Vol. 40)

and

FDA Direct Additives Limitations

(excerpts from the Code of
Federal Regulations, Vol. 21)

§ 180.104 Heptachlor and heptachlor epoxide; tolerances for residues.

Tolerances for total residues of the insecticide heptachlor (1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene) and its oxidation product heptachlor epoxide (1,4,5,6,7,8,8-heptachloro-2,3-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene) from application of heptachlor in or on raw agricultural commodities are established as follows:

0.1 part per million in or on cabbage, lettuce, rutabagas, snap beans.

Zero in or on alfalfa, apples, barley, beets (including sugar beets), blackeyed peas, brussels sprouts, carrots, cauliflower, cherries, clover, corn, cottonseed, cowpeas, grain sorghum (milo), grapes, grass (pasture and range), kohlrabi, lima beans, meat, milk, oats, onions, peaches, peanuts, peas, pineapple, potatoes, radishes, rye, sugarcane, sweet clover, sweetpotatoes, tomatoes, turnips (including tops), wheat.

§ 180.126 Inorganic bromides resulting from soil treatment with ethylene dibromide; tolerances for residues.

Tolerances for residues of inorganic bromides (calculated as Br) in or on raw agricultural commodities grown in soil treated with the nematocide ethylene dibromide are established as follows:

75 parts per million in or on broccoli, carrots, melons, parsnips, potatoes.

60 parts per million in or on eggplant, okra, summer squash, sweet corn, sweet corn forage, sweetpotatoes, tomatoes.

40 parts per million in or on pineapple.

30 parts per million in or on cucumbers, lettuce, peppers.

25 parts per million in or on cottonseed, peanuts (see § 180.126a).

10 parts per million in or on asparagus, cauliflower.

5 parts per million in or on lima beans, strawberries.

125 parts per million in or on soybeans.

[36 FR 22540, Nov. 25, 1971, as amended at 46 FR 15133, Mar. 3, 1981]

§ 180.138 Toxaphene; tolerances for residues.

Tolerances are established for residues of the insecticide toxaphene (chlorinated camphene containing 67 percent-69 percent chlorine) in or on raw agricultural commodities as follows:

7 parts per million in or on apples, apricots, beans, blackberries, boysenberries, broccoli, brussels sprouts, cabbage, carrots, cauliflower, celery, citrus fruits, collards, corn, cranberries, cucumbers, dewberries, eggplants; fat of meat from cattle, goats, hogs, horses, and sheep; hazelnuts, hickory nuts, horseradish, kale, kohlrabi, lettuce, loganberries, nectarines, okra, onions, parsnips, peaches, peanuts, pears, peas, pecans, peppers, pimentos, quinces, radishes (with or without tops) or radish tops, raspberries, rutabagas, spinach, strawberries, tomatoes, walnuts, youngberries.

5 parts per million in or on barley, oats, rice, rye, sorghum grain, wheat.

5 parts per million, calculated as a chlorinated terpene of molecular weight 396.6 containing 67 percent chlorine, in or on cottonseed.

3 parts per million in or on bananas (of which residue not more than 0.3 part per million shall be in the pulp after the peel is removed and discarded), pineapples.

2 parts per million in or on soybeans (dry form).

0.1 part per million in or on sunflower seeds.

[36 FR 22540, Nov. 25, 1971, as amended at 41 FR 22938, June 8, 1976; 51 FR 46662, Dec. 24, 1986]

§ 180.151 Ethylene oxide; tolerances for residues.

A tolerance of 50 parts per million is established for residues of the antimicrobial agent and insecticide ethylene oxide, when used as a postharvest fumigant in or on the following raw agricultural commodities: Black walnut meats, copra, whole spices.

§ 180.319 Interim tolerances.

While petitions for tolerances for negligible residues are pending and until action is completed on these petitions, interim tolerances are established for residues of the listed pesticide chemicals in or on raw agricultural commodities as follows:

Substance	Uses	Tolerance in parts per million	Raw agricultural commodity
[illegible]	[illegible]	0.1	Peanuts.
		0.05	Tomatoes.
		0.01	[illegible]
[illegible]	do	1	Alfalfa hay.
		0.05	Milk.

§ 180.397 Ethylene dibromide; tolerances for residues.

(a) A tolerance is established for the nematocide ethylene dibromide in or on soybeans at .001 part per million.

(b) A tolerance of 900 ppb (.9 ppm) for residues of ethylene dibromide per se is established on the following grains as a result of the use of EDB as a post-harvest fumigant prior to February 3, 1984: barley, corn, oats, popcorn, rice, rye, sorghum (milo), and wheat.

(c) Tolerances are established for residues of ethylene dibromide per se in or on the following raw agricultural commodities resulting from use of ethylene dibromide as a fumigant after harvest in accordance with the Mediterranean *Fruit Fly* Control Program or the Quarantine Program of the U.S. Department of Agriculture.

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Subpart B—Food Preservatives

§ 172.105 Anoxomer.

Anoxomer as identified in this section may be safely used in accordance with the following conditions:

(a) Anoxomer is 1,4-benzenediol, 2-(1,1-dimethylethyl)-polymer with diethenylbenzene, 4-(1,1-dimethylethyl)phenol, 4-methoxyphenol, 4,4'-(1-methylethylidene)bis(phenol) and 4-methylphenol (CAS Reg. No. 60837-57-2) prepared by condensation polymerization of divinylbenzene (m- and p-) with tert-butylhydroquinone, tert-butylphenol, hydroxyanisole, p-cresol and 4,4'-isopropylidenediphenol.

(b) The polymeric antioxidant meets the following specifications:

(1) Polymer, not less than 98.5 percent as determined by an ultraviolet method entitled "Ultraviolet Assay," 1982, which is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(2) Molecular weight: Total monomers, dimers and trimers below 500 not more than 1 percent as determined by a method entitled "Low Molecular Weight Anoxomer Analysis," 1982, which is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(3) Phenol content: Not less than 2.2 milliequivalent/gram and not more than 2.6 milliequivalent/gram as determined by a method entitled "Total Phenols," 1982, which is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(4) Heavy metals as lead (as Pb), not more than 10 parts per million. Arsenic (as As), not more than 1 part per million. Mercury (as Hg), not more than 1 part per million.

(c) Anoxomer may be safely used as an antioxidant in food at a level of not more than 5,000 parts per million based on fat and oil content of the food.

§ 172.155 Natamycin (pimaricin).

(a) Natamycin (CAS Reg. No. 7681-93-8), also known as pimaricin, is a polyene macrolide antimycotic substance possessing an empirical formula of $C_{33}H_{47}NO_{13}$ and a molecular weight of 665.7.

(b) The additive shall conform to the following specifications:

Purity: 97 percent ± 2 percent on an anhydrous basis.
Arsenic: Not more than 1 part per million.
Heavy metals (as Pb): Not more than 20 parts per million.

(c) The additive may be applied to the surface of cuts and slices of cheese to inhibit mold spoilage with the following limitations:

(e) To assure safe use of the additive:

(1) The label and labeling of the additive container shall bear, in addition to the other information required by the Act, the name of the additive.

(2) The label or labeling of the additive container shall bear adequate directions to assure use in compliance with the provisions of this section.

Subpart C—Coatings, Films and Related Substances

§ 172.210 Coatings on fresh citrus fruit.

Coatings may be applied to fresh citrus fruit for protection of the fruit in accordance with the following conditions:

(a) The coating is applied in the minimum amount required to accomplish the intended effect.

(b) The coating may be formulated from the following components, each used in the minimum quantity required to accomplish the intended effect:

(1) Substances generally recognized as safe for the purpose or previously sanctioned for the purpose.

(2) One or more of the following:

(3) In lieu of the components listed in paragraph (b)(2) and (4) of this section, the following copolymer and one or more of the listed adjuvants.

Component	Limitations
Vinyl chloride-vinylidene chloride copolymer	As an aqueous dispersion containing a minimum of 75 percent water when applied.

§ 172.399 Zinc methionine sulfate.

Zinc methionine sulfate, CAS Reg. No. 56329-42-1, may be safely used in accordance with the following prescribed conditions:

(a) The additive is the product of the reaction between equimolar amounts of zinc sulfate and DL-methionine in purified water.

(b) The additive meets the following specifications:

Zinc content—19 to 22 percent.
$C_5H_{11}NO_2S$ "DL-methionine"—46 to 50 percent.
Cadmium—not more than 0.05 part per million.

(c) The additive is used in tablet form as a source of dietary zinc.

[46 FR 58297, Dec. 1, 1981]

Subpart E—Anticaking Agents

§ 172.560 Modified hop extract.

The food additive modified hop extract may be safely used in beer in accordance with the following prescribed conditions:

(a) The food additive is used or intended for use as a flavoring agent in the brewing of beer.

(b) The food additive is manufactured by one of the following processes:

(1) The additive is manufactured from a hexane extract of hops by simultaneous isomerization and selective reduction in an alkaline aqueous medium with sodium borohydride, whereby the additive meets the following specifications:

(i) A solution of the food additive solids is made up in approximately 0.012 n alkaline methyl alcohol (6 milliliters of 1 n sodium hydroxide diluted to 500 milliliters with methyl alcohol) to show an absorbance at 253 millimicrons of 0.6 to 0.9 per centimeter. (This absorbance is obtained by approximately 0.03 milligram solids per milliliter.) The ultraviolet absorption spectrum of this solution exhibits the following characteristics: An absorption peak at 253 millimicrons; no absorption peak at 325 to 330 millimicrons; the absorbance at 268 millimicrons does not exceed the absorbance at 272 millimicrons.

(ii) The boron content of the food additive does not exceed 310 parts per million (0.0310 percent), calculated as boron.

(2) The additive is manufactured from hops by a sequence of extractions and fractionations, using benzene, light petroleum spirits, and methyl alcohol as solvents, followed by isomerization by potassium carbonate treatment. Residues of solvents in the modified hop extract shall not exceed 1.0 part per million of benzene, 1.0 part per million of light petroleum spirits, and 250 parts per million of methyl alcohol. The light petroleum spirits and benzene solvents shall comply with the specifications in § 172.250 except that the boiling point range for light petroleum spirits is 150°F–300°F.

(3) The additive is manufactured from hops by a sequence of extractions and fractionations, using methylene chloride, hexane, and methyl alcohol as solvents, followed by isomerization by sodium hydroxide treatment. Residues of the solvents in the modified hop extract shall not exceed 5 parts per million of methylene chloride, 25 parts per million of hexane, and 100 parts per million of methyl alcohol.

(4) The additive is manufactured from hops by a sequence of extractions and fractionations, using benzene, light petroleum spirits, methyl alcohol, n-butyl alcohol, and ethyl acetate as solvents, followed by isomerization by potassium carbonate treatment. Residues of solvents in the modified hop extract shall not exceed 1.0 part per million of benzene, 1.0 part per million of light petroleum spirits, 50 parts per million of methyl alcohol, 50 parts per million of n-butyl alcohol, and 1 part per million of ethyl acetate. The light petroleum spirits and benzene solvents shall comply with the specifications in § 172.250 except that the boiling point range for light petroleum spirits is 150° F to 300° F.

(5) The additive is manufactured from hops by an initial extraction and fractionation using one or more of the

§ 172.770 Ethylene oxide polymer.

The polymer of ethylene oxide may be safely used as a foam stabilizer in fermented malt beverages in accordance with the following conditions.

(a) It is the polymer of ethylene oxide having a minimum viscosity of 1,500 centipoises in a 1 percent aqueous solution at 25° C.

(b) It is used at a level not to exceed 300 parts per million by weight of the fermented malt beverage.

(c) The label of the additive bears directions for use to insure compliance with paragraph (b) of this section.

§ 172.859 Sucrose fatty acid esters.

Sucrose fatty acid esters identified in this section may be safely used in accordance with the following prescribed conditions:

(a) Sucrose fatty acid esters are the mono-, di-, and tri-esters of sucrose with fatty acids and are derived from sucrose and edible tallow or hydrogenated edible tallow or edible vegetable oils. The only solvents which may be used in the preparation of sucrose fatty acid esters are those generally recognized as safe in food or regulated for such use by an appropriate section in this part. Ethyl acetate or methyl ethyl ketone or dimethyl sulfoxide and isobutyl alcohol (2-methyl-1-propanol) may be used in the preparation of sucrose fatty acid esters.

(b) Sucrose fatty acid esters meet the following specifications:

(1) The total content of mono-, di-, and tri-esters is not less than 80 percent as determined by a method title "Sucrose Fatty Acid Esters, Method of Assay," which is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(2) The free sucrose content is not more than 5 percent as determined by Test 8.2 in the method titled "Sucrose Fatty Acid Esters, Method of Assay," which is incorporated by reference. The availability of this incorporation by reference is given in paragraph (b)(1) of this section.

(3) The acid value is not more than 6.

(4) The residue on ignition (sulfated ash) is not more than 2 percent.

(5) The total ethyl acetate content is not more than 350 parts per million as determined by a method titled "Determination of Ethyl Acetate," which is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(6) Arsenic is not more than 3 parts per million.

(7) Total heavy metal content (as Pb) is not more than 50 parts per million.

(8) Lead is not more than 10 parts per million.

(9) The total content of methyl ethyl ketone or of methanol shall not be more than 10 parts per million as determined by a method titled "Methyl Ethyl Ketone Test; Methyl Alcohol Test," which is incorporated by reference. Copies are available from the Division of Food and Color Additives, Bureau of Foods (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office

PART 193—TOLERANCES FOR PESTICIDES IN FOOD ADMINISTERED BY THE ENVIRONMENTAL PROTECTION AGENCY

Subpart A—Food Additives Permitted in Food for Human Consumption

§ 193.200 Ethylene oxide.

Ethylene oxide may be safely used as a fumigant for the control of microorganisms and insect infestation in ground spices and other processed natural seasoning materials, except mixtures to which salt has been added, in accordance with the following prescribed conditions:

(a) Ethylene oxide, either alone or admixed with carbon dioxide or dichlorodifluoromethane, shall be used in amounts not to exceed that required to accomplish the intended technical effects. If used with dichlorodifluoromethane, the dichlorodifluoromethane shall conform with the requirements prescribed by § 173.355 of this chapter.

(b) To assure safe use of the additive, its label and labeling shall conform to that registered with the U.S. Environmental Protection Agency and it shall be used in accordance with such label or labeling.

(c) Residues of ethylene oxide in ground spices from both postharvest application to the raw agricultural commodity whole spices and application to the ground spices shall not exceed the established tolerance of 50 parts per million for residues in whole spices in 40 CFR 180.151.

[40 FR 14156, Mar. 28, 1975. Redesignated at 41 FR 26568, June 28, 1976, and amended at 50 FR 2958, Jan. 23, 1985]

§ 193.450 Toxaphene.

A tolerance of 6 parts per million is established for residues of the insecticide toxaphene (chlorinated camphene containing 67 to 69 percent chlorine) in crude soybean oil when present therein as a result of the application of this insecticide to the growing soybean crop.

[51 FR 46617, Dec. 24, 1986]

APPENDIX C

Conversion of Parts per Million (ppm) to Micrograms per day (µg/d)

1 ppm = 1 microgram of pesticide/ gram of food product

Thus, 1 ppm of pesticide on a food product = 1 µg of pesticide ingested, per gram of that food consumed.

If food consumption is expressed in grams per day (g/d), and the level of pesticide on that food is expressed in parts per million (ppm), then the amount of pesticide consumed per day = ppm x g/d

Example: 10 ppm = 10 µg/ g of food x 100 g of food/day = 1000 µg/day of pesticide ingested

RESPONSES OF DAVID ROE TO QUESTIONS ASKED BY SENATOR KENNEDY

1) [Changed industry attitudes toward Proposition 65; reasons for change]

Although it would be a considerable exaggeration to say that industry now generally "has come to support" Proposition 65 in the three years since its enactment, it is fair to say that leading industries and industry groups have radically changed the content and tone of their public positions toward to the new law.

In large measure this is due to the fact that a wide range of catastrophic predictions about Proposition 65's effect, which formed the basis of most of industry's pre- and post-vote opposition, have been disproven by the passage of time. In the words of California's top Proposition 65 regulatory official, Thomas Warriner, "the sky is not falling." Industry statements were once commonplace that Proposition 65 would be "Draconian," "unworkable," and/or "unfair." Now they are rare. EDF believes that this reflects the actual operation of the new law in practice, and the fact that large segments of industry are publicly acknowledging that they can live within Proposition 65's boundaries without any kind of significant disruption of their activities--as long as they accept the "self-policing" and quality control responsibilities implicit in the statute.

Food is a special case, and requires a different answer. The food industry, represented by national lobbying associations based in Washington, D.C., has conducted an all-out campaign against Proposition 65 since the law was enacted, and is still strenuously and publicly opposed to the act.

For carcinogens in food, there is no actual experience yet with the operation of the law, because the industry successfully lobbied an exemption for their products (foods, drugs, cosmetics and medical devices) into state regulation just before the law took effect in February 1988. Thus, a significant-risk level of a carcinogen in a food product which does not contain a warning would not today violate Proposition 65, even though the same level of carcinogen exposure in any other form (e.g., a non-food consumer product) would violate the law and would require a warning.

Because there has been no actual operating experience under Prop. 65 for carcinogens in foods, drugs, cosmetics, and medical devices (the extent of the exemption), the process described above for other industries has not yet taken place for the food industry. The food industry has also strenuously sought to obtain federal preemption of Prop. 65, and its lobbyists have promised their clients that this effort will succeed. Therefore, the food industry in general has not prepared itself for the day when the law will go into effect for carcinogens in their products. Since federal preemption has now been definitively rejected by the Bush Administration, this may soon change.

In addition, the Committee should be aware that the regulatory exemption (contained in 22 California Code of Regulations Section 12713, and covering all foods, drugs, cosmetics, and medical devices) is currently under legal challenge by a coalition of Prop. 65 proponents including the Environmental Defense Fund, and a legal ruling is expected soon.

2) [Application of Proposition 65-type requirements to federal regulation of pesticide residues]

S. 722 imposes an across-the-board negligible risk standard for pesticide chemical residues in processed food. As policy, this is quite consistent with Proposition 65.

However, the structure of S. 722 as introduced fails to take advantage of burden-shifting mechanisms which are central to the Proposition 65 approach. At each of the important steps in the process, S. 722 relies on action by the Administrator (e.g., determination of negligible risk standard for individual pesticides; evaluation of existing data; determination of inadequate data for pre-existing tolerances). Thus, if the Administrator fails to act, the protections of the law are not operative. Twenty years of history indicates that this will often be the case.

Proposition 65 creates legal consequences and puts its protections into effect whether or not government regulators have acted. It does so by setting out a standard very similar to the negligible risk standard in S. 722, but requiring *industry* to bear the burden of proof in showing compliance with that standard, independent of whether the standard has been quantified for individual chemicals or otherwise refined by regulation. Thus, industry is at risk from the day the law takes effect, and may not take shelter behind regulatory inaction.

Ironically, this has had the effect in California of dramatically improving the speed and precision of the regulatory process: since industry *is* at risk, it becomes in industry's interest to secure precise regulatory definitions, on a prompt timetable, so that certainty of compliance can be assured.

A similar mechanism could be used in S. 722 to meet its announced goals. All residues in excess of the negligible risk standard (as defined) could simply be deemed to violate the statute, whether or not specific tolerances meeting the S. 722 standard were in effect, had been reviewed, etc. Exceptions would be available only on the basis of positive action by the Administrator, and only in conformity with the statutory standard. All references to Administrator action would have to be changed to indicate that such action was discretionary rather than mandatory.

A question that needs to be addressed directly: what consequences should the law impose on non-complying food products? One answer--the one currently contained in S. 722--is that the products should be removed from the market. This is consistent with current FDCA law and with protection of the public health. However, the very nature of this "ultimate penalty" might make it politically unpalatable to enforce in practice, particularly if it were applied in situations where the burden of proof had been shifted, and thus where the penalty could be imposed in a wider variety of circumstances than at present. One alternative option is be that non-complying food products could be required to bear a label that stated: "WARNING: this product contains pesticides and does not meet federal pesticide standards for food." Though less severe than a ban, this consequence would be likely to create a powerful marketplace incentive to speed up products testing by individual manufacturers (as well as cooperation by those manufacturers in tolerance-setting) in order to avoid the warning. Removal from the market would still be the consequence for a product that was shown to exceed a specific tolerance (as under S. 722 in present form).

The final question that must be considered is the enforcement mechanism. This is addressed below.

Based on experience under Proposition 65 to date, the mechanisms described above are likely to provide substantially greater assurance of product-by-product safety than the requirements currently imposed through EPA and FDA. One conspicuous food example is available (since Prop. 65 is currently in effect for *reproductive toxins* in foods): the California law has succeeded in getting lead-soldered cans removed from the California market (lead is a known reproductive toxin). This welcome development took place just before Prop. 65 went into effect, and was voluntarily initiated by industry in order to avoid the warning requirement for lead. No formal enforcement action was required.

3) [Enforcement provisions]

No citizen suits have been filed under Prop. 65 with respect to food products (presumably because of the regulatory exemption described above); and only a handful of Prop. 65 citizen suits have been filed overall. However, the threat of direct citizen suit enforcement appears to have been a crucial element in securing voluntary industry compliance, and industry's self-policing, at the pre-enforcement stage. The lead-in-cans experience described above is a representative example. Industry appears to be far more scrupulous about preventing toxics exposures when it faces the threat of citizen enforcement under Prop. 65 than when it faces enforcement by, e.g., EPA.

The one citizen enforcement action commenced by EDF under Prop. 65, against national manufacturers of non-cigarette tobacco products, was quickly and completely successful in forcing warnings onto those tobacco products that had escaped federal regulation for more than 20 years. Under a court-approved settlement, reached less than three weeks after the suit was filed, all such products now bear conspicuous cancer warnings in California (and, reportedly, throughout the nation as well).

A similar provision could be incorporated into federal controls of food safety, for specified types of violations. However, several caveats are appropriate. First, citizen-suit enforcement backed by fines, with a portion of the fines retained by the successful plaintiff as provided in Prop. 65, has generated intense controversy from industry. This controversy appears to have taken a life of its own, since it is being fed even by industries (such as the food industry) that claim all their products would fall within compliance standards in any case and would therefore not be subject to enforcement actions. A credible threat of citizen suit enforcement raises the possibility that all violators are at risk, rather than simply the largest, most persistent, or most impolitic violators, as is usually the case under government agency enforcement. Industry appears to have a strong preference for the latter.

Second, citizen suit enforcement is an effective mechanism only to the extent that such suits are easy to bring and win when violations exist. For this purpose, the burden-of-proof shift is crucial. Citizen suit provisions in conventional toxics laws, where plaintiffs are required to prevail on complex scientific issues in order to obtain enforcement, e.g., the Resource Conservation and Recovery Act (illegal hazardous waste disposal), have been largely ineffective in practice.

A credible citizen suit mechanism appears to be highly effective in creating incentives for universal compliance. Various options are available to tailor this mechanism to achieve desired ends, including variations in incentives for enforcers and the consequences of successful enforcement action. Industry rhetoric about "overwhelming the courts" with "bounty hunter" actions, which has been a staple of the debate in California for the last three years, should be evaluated in light of the actual experience under Prop. 65 with citizen suit enforcement in the first 14 months of the statute's operation.

Senator HATCH. Well, I agree with you. I hope we can come up with a uniform approach to solve this problem, with the Administration's support. If we cannot do that, then I think the Administration has to do a pre-emption. I think that we will move that way ultimately, unless we can come up with a consensus bill that does the job. I think we can, and I think there has been support here showing that we can.

Dr. Booth, let us finish this hearing with your testimony. If you can present it in about five minutes, we would appreciate it.

Let me apologize for Senator Kennedy. He has to be at his caucus. He hated to leave. What we will do is listen to your testimony, and then turn this hearing over to the staff so that they can ask you some very good questions.

Dr. BOOTH. Thank you.

As the Senator indicated, I am Gary Booth. I am the director of the Toxicology Research Laboratory of Brigham Young University, have been there for the past 15 years, and have been involved in doing research on chemicals, particularly pesticides, for about 20 years. That has involved upwards to nine different States where we have actually had to go out and actually measure these residues, not only in our foodstuffs but in a variety of matrices, including soil, water, plants, animals. We have concluded that this kind of research has to be done. We spent a great deal of time designing experiments so that the data can be reliable. There has been, in my opinion, too much anecdotal information and a lot of testimony without substance of data. So I would say that in the past 20 years we are learning.

Pesticides are not the only issue. We have data, for example, on fossil fuels that would make pesticides look as safe as mother's milk. And we have got publications that we would be happy to show at some point. But pesticides are the issue today, and we need to address them.

I would make the following eight points. First of all, we have heard testimony on risk assessment. We know it is important. All of us who are toxicologists believe in that. But it may be inappropriate to lock science into some sort of a given date. We know that these biological end points that we are measuring in the laboratory and field are changing, and I do not think we can afford to make the same mistakes that we made with DDT 50 years ago.

Second, the risk/benefit analysis has already been addressed. I will not go over that, except that somehow there needs to be some provision for emergency situations. In 1972, I was in this town and testified at the DDT hearings, and that same provision had to be allowed for certain kinds of emergency situations which we know can occur in agriculture.

Third, the inerts issue is not a new issue. We have been studying it for the past five years in our laboratory. They need to be evaluated, but you have got to be very careful about how you design those experiments. The timetable can be almost overwhelming if you look at the expense and the manpower needed.

Fourth, and I think this is an underlying point, there is going to be a serious shortage of scientists and science resources by the tasks that this bill is going to create. Right at the moment, we have data to show that food scientists and toxicologists are at a deficit. We will never be able to handle the workload if this bill goes in as it is.

Fifth, uniform food standard in terms of risk has already been addressed. Senator Cochran has mentioned this and Senator Hatch, also. I do not think we can afford to have one State contend with another. We have to have a number, a uniform predictive number that is reliable for all States.

Sixth, the food supply and cost of food, the serious shortages that these compounds could occur I think are real. I do not think they are imaginary, and they could indirectly—and I repeat, indirectly—affect the health of this Nation.

Because of that point, I would add, number seven, that the food shortage and increased costs could negate the purchasing power of a certain segment of our population. And I would re-emphasize that there are some serious health effects because of an imbalanced diet that could backlash from lack of certain compounds needed.

I believe, and I will go down on record as believing this, that every American ought to have access to a balanced diet that would include moderation, variety, and certainly an opportunity to have balance in his diet. We published a book in 1986 "Toward a Healthier Life Style," and we have a chapter on diet and cancer that suggests that diet is playing an increasingly important role in preventing some forms of cancer.

Finally, point eight, I do not need to say this perhaps, but I think I will, anyway, that those of us who are in science accept the responsibility. We know that there is some good science being done, and it is changing. But I would recommend that we continue using good laboratory procedures. There have been a lot of mistakes made in science, and I think the goals that are asked for in 722 are perhaps somewhat unrealistic, but I think the public has the right to a good data base, something that is reliable, that they do not have to read about and wake up like we did with the DDT action.

I believe as far as the experiments that have to be performed, there is going to be a horrendous amount of effort in that regard. I have calculated just in one single compound, if you look at the inerts and maybe even the synergism of different compounds, that over 600 experiments will be required for every data point. I would just add the cautionary note that if we are going to deal with the science issues, we have to deal with them at the wet bench and in the field.

Thank you.

Senator HATCH. Well, thank you. I want to thank all three of you for your testimony here today. I think this has been a very important hearing. I think people are starting to realize how important this issue is. We have been trying to get people on both sides of this issue now for years to look at it and look at it carefully. Although I do not want to have 50 different State actions on this matter, I have to say that your work on Proposition 65 has fomented this issue in a way that we were never able to do in the past years. So, in a sense, whether people agree with you or disagree with you, Mr. Roe, you have done this country a great service in bringing this to a head, and it has to be brought to a head. I just hope that you will work with us to try and come up with a uniform approach to resolve these problems. If we can, then everybody is going to be better off.

Mr. ROE. Thank you very much for those comments, Senator. I look at this as the first conversation in a dialogue that will go on for some time, and I hope be very productive for the country as a whole.

Senator HATCH. I hope that is true.

Well, I am going to turn the dais over to majority and minority counsel to make the rest of the record in this matter, with the understanding that we have got these conflicts. We hope you will forgive us for having to leave. Thank you. We will turn it over to Dr. Keith.

Dr. KEITH. [Presiding.] Thank you.

Before we proceed to questions, we might receive testimony from Ellen Haas from Public Voice and Sherwin Gardner from the Grocery Manufacturers Association.

STATEMENTS OF ELLEN HAAS, EXECUTIVE DIRECTOR, PUBLIC VOICE FOR FOOD AND HEALTH POLICY, WASHINGTON, DC; AND SHERWIN GARDNER, VICE PRESIDENT FOR SCIENCE AND TECHNOLOGY, GROCERY MANUFACTURERS OF AMERICAN, INC., WASHINGTON, DC

Ms. HAAS. Thank you very much. I am Ellen Haas, executive director of Public Voice for Food and Health Policy.

Ever since our beginning, we have worked for access to a safe, nutritious and affordable food supply. For that reason, we are particularly pleased to be here to offer our thoughts on S. 722, a bill that we believe would provide much needed enhanced protection against the unnecessary risks posed by pesticide residues in food.

I do not often object to Dr. Benbrook. In fact, I think his work has been exceptional in this field. However, I believe that being an aggressive bill is something that is very positive and what is needed for consumer protection at this time.

Throughout our six-and-a-half year history, we have worked for the adoption of strong food safety policies that would remove unnecessary risks from the food supply, such as those posed by pesticide residues. The cornerstone of our approach to food safety policy is the principle that consumers should not be—and do not want to be—exposed to the risk of serious health problems, such as cancer, that can be avoided, that are involuntary, and that do not result from natural causes.

We support S. 722 because it would incorporate into the regulatory process long overdue requirements that EPA take steps to reduce, in an expeditious manner, the unacceptable health risks posed by pesticide residues in food. Because EPA has failed under the existing regulatory framework to adequately address the unacceptable risks of pesticide residues in food, we believe that strong new regulatory legislation is urgently needed.

There is no better indicator of this regulatory failure than the crisis of public confidence that has been building in the 1980's. It is not just a new phenomenon of 1989, but it, rather, goes back some time. At a recent food forum that we convened with the League of Women Voters and that was attended by all parts of the food system—from growers to food retailers, food manufacturers, consumer advocates, environmentalists—there was total agreement that restoring public confidence in the safety of our food is our biggest challenge. Food marketing institute surveys have showed that from 75 to 80 percent of food consumers feel that pesticide residues pose a serious health hazard. We also believe that the public's concerns are justified and do not merely reflect, as many have said today and for many months, that these are false perceptions.

According to the FDA, in 1987 43 percent of all U.S. food shipments contained pesticide residues. The fact that most of those residue levels did not exceed tolerances is little comfort since the majority of tolerances have been set without adequate health and exposure data. In addition, the EPA lists 66 active ingredients in pesticides as proven animal carcinogens and considers 25 of them to be probable human carcinogens. In 1987, the NAS estimated that the oncogenic risks posed by pesticides from 28 of those animal carcinogens were significant, and that those risks could be reduced substantially if a new health-based regulatory framework would be adopted.

What makes S. 722 such a potential public-confidence builder is that it follows these recommendations and replaces EPA's current use of risk/benefit analysis with a risk-only, negligible-risk standard for granting and setting tolerances. By eliminating EPA's ability to consider economic benefits when granting tolerances, the bill would depoliticize the regulatory process and would prevent the Agency from using its discretion to place the interests of industry against the health of consumers as it has done.

Risk/benefit analysis is also problematic because it is a highly subjective procedure that has no place in a science-based regulatory scheme. And EPA is not likely to develop the needed kinds of scientific rigorous analysis that is needed here because the nature of the comparison of two incommensurable things such as health risks and economic benefits ensures that the weighing process will always be inherently subjective.

Furthermore, the bill would enhance the credibility of the tolerance-setting process as a safeguard to public health. At present, the tolerance-setting procedure omits critical factors that contribute to the health risks posed by pesticide residues. To correct these inadequacies, the bill would require explicitly that EPA account for all avenues of exposure.

Confidence in the tolerance-setting process is also currently undermined by the fact that many tolerances were set without the use of adequate health effects data. A 1982 report by the House Agriculture Subcommittee—and still really reflective of today's situation—estimated that 84 percent of registered pesticides lack adequate cancer tests. To correct this problem, the bill would authorize EPA to require the submission of necessary data to support each tolerance.

Although we strongly support the bill, as we have stated, we believe that the public's interest needs to be further served by strengthening in three major ways:

First of all, we recommend a phase-out period for pesticides that have been found to be animal or human carcinogens should be included. Then, as previously stated, we feel that there needs to be an explicit prohibition of Federal pre-emption of State pesticide residue regulations. Third, we believe that specific requirements for FDA's monitoring of the safety of imported foods should be detailed.

In conclusion, we believe that a strengthened S. 722 can make the most of an unprecedented opportunity to genuinely improve the safety of the food supply where it is needed. The public is ready and eager to support such initiatives that meet public health objectives, and now we need to get down to work.

Thank you.

[The prepared statement of Ms. Haas along with responses to questions asked by Senator Kennedy follows:]

PREPARED STATEMENT OF ELLEN HAAS

Chairman Kennedy and members of the committee, my name is Ellen Haas. I am the executive director of Public Voice for Food and health Policy, a nonprofit research, public-policy education and advocacy organization that focuses on food safety, health and nutrition issues. We are pleased to have been invited to appear before the committee today to offer our thoughts on S. 722, The Food Safety Amendments of 1989, a bill that would provide consumers with much-needed, enhanced protection against the unnecessary risks posed by pesticide residues in their food.

Since 1983, when we released our report entitled, "A Market Basket of Food Hazards: Critical Gaps in Government Protection," Public Voice has been documenting the unacceptable health risks posed by pesticide residues and the inadequacies of government protection against those risks. Throughout our six-and-one-half-year history we have worked for the adoption of a strong federal food-safety policies that would remove sources of unnecessary risks from the food supply, be they pesticide residues, microbial contaminants in livestock, poultry and fish products, or chemical contaminants in fish, seafood and meat.

The cornerstone of our approach to food safety policy is the principle that consumers should not be--and do not want to be--exposed to the risk of serious health problems, such as cancer, that can be avoided or be removed, that are not of their own choosing, and that are the result of technology as opposed to natural causes. Since health risks posed by pesticide residues are avoidable, are involuntary, and are not of natural origin, we feel that they are unacceptable and should be reduced substantially.

We support S. 722 as a giant step in the right direction because it would incorporate into the pesticide regulatory process long-overdue requirements that EPA take steps to reduce, in an expeditious manner, the unnacceptable health risks posed by pesticide residues in food. In addition, we are pleased that S. 722 is addressing concerns about pesticide residues in food as a food-safety question within the Federal Food, Drug and Cosmetic Act (FFDCA) rather than only as a pesticide-registration issue under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Because the existing federal regulatory regime under FIFRA cannot adequately address the unacceptable risks of pesticide residues in foods, strong, new regulatory legislation such as S. 722 is urgently needed.

There is no better indicator of this regulatory failure than the crisis of public confidence that has been building throughout the 1980s. Annual surveys by the Food Marketing Institute have shown consistently that 75-to-80 percent of food consumers feel that pesticide residues pose a serious health hazard. In late April of this year, Public Voice and the League of Women Voters sponsored a forum on pesticide residues as part of our Food Forum Education Project. Thirty representatives from consumer and environmental organizations, the supermarket, agrichemical, food processing and fresh produce industries, and government regulatory agencies particpated in the forum. They agreed that the biggest challenge facing us is the deterioration of public confidence in the safety of food and in the government agencies that regulate pesticide residues.

All too often the standard response to the confidence problem--as well as to consumer reactions to incidents involving pesticides like Alar--is that consumer concerns reflect false perceptions of risk, and that the real risks are at worst insignificant.

In reality, consumers' concerns are quite justified. In 1987, according to FDA, forty-three percent of all U.S. food shipments contained pesticide residues. The actual extent of residues may be greater since FDA's multi-residue methods cannot detect nearly half of all pesticides currently in use. Also, individual food products often reflected a much higher-than-average incidence of residues in the 1987 study. For example, residues were found in eighty-two percent of the samples of strawberries and sixty-nine percent of the samples of grain products. Fungicides, which are used heavily on these products, are considered to be the most toxic category of pesticides. The fact that most of those residue levels did not exceed tolerances is little comfort since the majority of tolerances have been set without adequate health and exposure data.

In addition, the EPA lists sixty-six active ingredients in pesticides as proven animal carcinogens, and considers twenty-five of them to be "probable human carcinogens." In 1987, The National Academy of Sciences Board on Agriculture, in their study Regulating Pesticides in Food, examined the oncogenic risk to humans posed by twenty-eight of those animal carcinogens. They estimated that the risks posed by residues from those pesticides were significant, and that those risks could be reduced substantially if a new, health-based regulatory framework would be adopted.

What makes S.722 such a potential public-confidence builder is that it follows the recommendation of the NAS study and effectively replaces EPA's current use of risk-benefit analysis with a risk-only, negligible-risk standard for granting and setting tolerances. For years, EPA officials have complained that they cannot always act expeditiously in the interests of public health to remove food-safety hazards because their hands are tied by existing legislation. We would suggest that the best way for Congress to respond to this problem is to enact legislation that removes the burden of having to weigh the economic benefits from pesticide use against the health risks posed by pesticide residues. S. 722, by eliminating EPA's ability to consider economic benefits when granting tolerances, would depoliticize the regulatory process and prevent the agency from placing the interests of industry ahead of the health of consumers. In so doing, S. 722 would remove one of the major sources of the public-confidence problem.

Aside from undermining public confidence, risk-benefit analysis is problematic because it is a highly subjective procedure that has no place in a science-based regulatory regime. As Jack Moore, EPA's deputy administrator stated three weeks ago in testimony before the Subcommittee on Health and the Environment of the House Energy and Commerce Committee EPA has not been able to develop a rigorous, scientific approach to determining how economic benefits should be weighed against health risks. And EPA is not likely to be able to do so, because the nature of the comparison of two incommensurable things such as health risks and economic benefits ensures that the weighing process will always be inherently subjective, discretionary, and therefore potentially political. This kind of decision process does not belong in a regulatory regime that we all think should rely on rigorous, science-based procedures.

S. 722 would also enhance the credibility of the tolerance-setting process as a safeguard to public health. At present, it is difficult to argue that residues below tolerance levels are safe --as industry and government agencies have been doing--since the current tolerance-setting procedure omits critical factors that contribute to the health risks posed by pesticide residues. To correct these inadequacies, the bill would require explicitly that EPA use more realistic and conservative tolerance-setting methods. Among other things, it would ensure that for the first time tolerances would account for exposure to the pesticide from all sources, exposure of special groups like preschoolers with unique consumption patterns, and exposure to toxic inert ingredients used in pesticide formulations.

Confidence in the tolerance-setting process is also currently undermined by the fact that many existing tolerances were set without the use of adequate data on the health effects of the pesticide residues. A 1982 report by the House Agriculture Subcommittee on Department Operations, Research and Foreign

Agriculture estimated that eight-four percent of registered pesticides lack adequate cancer tests, seventy percent lack proper testing for birth defects and ninety-three percent lack adequate tests for genetic mutations. To correct this problem, S. 722 would authorize EPA to require the submission of necessary data to support the tolerance. We would recommend, however, based on EPA's historical inability to act expeditiously in these matters, that deadlines for the submission of data be made explicit in the bill rather than be left to the discretion of EPA.

Mr. Chairman, although as I have indicated we strongly support S. 722 as a means of reducing unnecessary risks, we believe that the public's interest will further be served if the bill is strengthened in three major ways:

Phase-out of Carcinogens. We recommend that the bill include a phase-out period for pesticides that have been found to be animal or human carcinogens. The bill, as it is currently written, provides that after six years, residues of a number of animal and probable human carcinogens can exist in food as long as the combined risk from exposure to those residues meets the negligible-risk criterion. Given the uncertainties involved in risk-assessment procedures, we feel that the best way to ensure that unnecessary risks are eliminated would be to phase out pesticides that are animal or human carcinogens by the end of the next decade. Such a phase-out requirement would provide additional incentives, beyond those already provided for by the implementation requirements of

S. 722, for the private sector to devote substantial time, energy and financial resources to the development of nontoxic alternative technologies and practices. The relatively small effort currently being made to develop nontoxic pest-control methods suggests that stronger regulations are needed to encourage private-sector action.

Prohibition of Preemption. An explicit prohibition of federal preemption of state pesticide-residue regulations must be included in the bill. Arguments for preemption of state laws that are made in the absence of support for the strongest possible federal food safety laws are not particularly convincing. For there is no better way to remove the need for strong state laws than to have strong federal protections. With continuing gaps in federal protections, the ability to enact strong state regulations provides an indispensable public safeguard against the risks posed by pesticide residues.

Explicit Requirements for Imported Foods. The bill, as currently written, does not address the problems associated with residues in imported food products. FDA's monitoring of residues and enforcement of tolerances for imported foods have been roundly criticized by GAO and public-interest organizations. Given the large proportion of fresh produce, particularly in the winter months, that originates in countries that do not regulate pesticides nearly as stringently as we currently do in this country, special steps should be taken to ensure that imported produce meets the same public-health standards required of domestically grown produce. Since pesticide-use is not regulated uniformly across countries, the burden of protecting U.S. consumers will have to be placed disproportionately on FDA's monitoring of residues and enforcement of tolerances. Given FDA's track-record when regulation of imported foods has been left largely to their discretion under the existing FFDCA, we believe that S. 722 needs to specify precisely what FDA will be required to do to ensure the safety of imported foods.

Conclusion

By passing a strengthened S. 722 Congress can make the most of an unprecedented opportunity to genuinely improve the safety of the food supply where it is needed. The public is ready and eager to support new federal efforts that will reduce substantially the unnecessary risks posed by pesticide residues. Consumers are looking to Congress to lead the way with strong new legislation that will enable them to have full confidence that their food is safe. A strengthened S. 722, which will require EPA to act in the public's interest, is necessary if we hope to achieve the public-health objectives that we all share.

RESPONSES OF ELLEN HAAS TO QUESTIONS ASKED BY SENATOR KENNEDY

1. PREEMPTION OF STATE LEGISLATION:

I believe that if a strengthened S. 722 is passed and proves to be faithfully executed by EPA and FDA, there would be little need to be concerned about negative consequences of "a variety of conflicting laws in the states."

To the extent that federal legislation needs strengthening, consumers will continue to be exposed to unnecessary risks and the conditions for the passage of strong state legislation will therefore remain. Those who are concerned that state laws might create regulatory problems, will thus want to avoid weakening the consumer protections in S. 722. The passage of national legislation that uses a strict, health-based, risk-only standard and that requires regulatory agencies to implement well-specified provisions would remove many of the conditions that have given rise to a variety of state measures that regulate pesticide residues.

Nonetheless, by itself, strong federal legislation has never been enough to ensure that consumers will be protected from food hazards. EPA's failure to implement existing food-safety regulations and FDA's inability to monitor pesticide residues adequately demonstrate that strong legislation is no guarantee that consumers will be protected against unnecessary risks posed by pesticide residues. That is why the public should always have recourse to state legislation regardless how strong federal pesticide-residue legislation might be. The potential for states to pass and implement strong legislation of their own thus represents a necessary safeguard against the threat of inadequate implementation on the part of federal regulatory agencies.

Thus, to the extent that either federal pesticide-residue legislation or regulation are not adequate to protect the public from unnecessary risks, the ability of states to pass and implement strong pesticide-residue laws will remain an important vehicle for achieving food-safety objectives. For this reason, I very strongly believe that federal legislation that preempts state pesticide-residue regulation would not serve the public interest and should not be considered.

2. REDUCTION OF THE NECESSITY OF PESTICIDES.

Public Voice's Food Forum on Pesticide Residues. Last April, Public Vocie held a Food Forum on pesticide residues in which alternatives to conventional pest-control methods and policies that affect the development and adoption of those methods were discussed. The Food Forum is an annual component of our three-year Food Forum Education Project, which is supported by the Kellogg Foundation and is administered jointly with the League of Women Voters Education Fund. Since the forum was geared primarily toward the development of policy options that need to be communciated to the public, the technical aspects of the array of available alternatve approaches were not discussed in great detail.

Status of Efforts to Reduce Dependence on Toxic Pesticides. It appears that the major thrust of efforts to reduce dependency on toxic pesticides has occurred at the individual-farm level. In response to the high dollar and environmental costs of chemical-intensive farming and consumer concerns about the safety of pesticde residues, some producers have taken steps to implement alternative pest-control methods. Integrated pest management programs have enabled farmers to reduce pesticide-use by 20 to 50 percent for some crops, and IPM methods are being used on more than 30 million acres. However, most IPM methods available are for control of insect pests; very little work has been done on alternative weed and disease control for major commodities such as corn, soybeans, wheat and rice. Despite the acceptance of IPM as a legitimate method, IPM has not been adopted to the extent that it has had much effect on the total use of pesticides in agriculture.

The innovative efforts of individual farmers have been complemented primarily by public-sector support at the state level. Programs to promote the development and adoption of alternative methods have been implemented in a host of states such as California, texas, Iowa, Minnesota, Wisconsin, Vermont and Maine. Measures include: taxes on agrichemical sales to finance development of alternatives; low-interest loans for the adoption of alternative technologies; research and education programs; information-dissemination projects; funding for market research; and programs to certify producer claims about pesticide use.

What Can The Federal Government Do? The first component of a program to promote safer alternatives is a strong regulatory program that removes unnecessary risks posed by pesticide residues. As I stated in my written testimony, the federal government can increase the incentive for the development of alternative methods by strengthening regulatory legislation concerning tolerances, by ensuring that the laws are faithfully executed, and by providing for better monitoring and enforcement of tolerances. Existing pesticide legislation and the regulatory agencies' history of protecting agriculture from consumers, rather than vice versa, has consistently sent signals to agriculture that there is no need to develop alternatives. The absence of strong regulatory action has in effect legitimized and promoted the continued development of and dependence on the use of toxic pesticides in agriculture. Because S. 722 will make it much more difficult to legally use hazardous pesticides, it will stimulate the search for nonhazardous alternatives.

The second component of a federal effort should be the establishment of a crash program to enhance the country's ability rapidly develop and adopt alternative pest-control methods. Insufficient funding levels for the LISA program and the failure of USDA to integrate the development and transfer of alternative technologies into its research and extension infrastructure ensure that the development and adoption of alternative technologies will, at best, proceed very slowly.

The third component should include measures to remove the incompatibility between food-safety objectives and some of the provisions of federal farm price- and income-support programs. There is widespread agreement that a number of provisions of the commodity programs of the Food Security Act of 1985 create incentives for the continued use of conventional pest-control methods.

Lastly, the federal government should recognize the important role that food markets play in farmers' choices among pest-control methods. Nowhere has the pressure to intensify pesticide-use been more apparent than in fresh-produce markets where cosmetic quality standards are all-important competitive factors. Even now, despite concerns about the hazards posed by pesticide residues, food markets remain biased toward continued pesticide-use and have generally failed to respond to consumer concerns about pesticide residues with safer products.

The federal government contributes to this bias through its standards for food grading and marketing orders. Federal grading standards for many commodities provide a direct incentive for pesticide-use by emphasizing cosmetic quality, and create a direct disincentive for the adoption of alternative technologies by not differentiating products on the basis of their food-safety qualities. Federal marketing orders are worse in that they often use cosmetic standards to regulate the supply of the commodity that enters the market.

To address these problems, the federal government should prohibit the use of cosmetic standards as supply-control mechanisms in marketing orders and change federal grading standards to reflect consumer concern about pesticide residues. Marketing-order policies could be redesigned to provide producers with market incentives to adopt alternative approaches, and new grading standards could be developed to reflect the enhanced food safety that results from the use of alternative pest-control methods.

3. IMPROVED MONITORING OF IMPORTED FOODS

The need for improving FDA's program for monitoring food imports for illegal pesticide residues has been well-documented by the General Accounting Office and numerous Congressional hearings on the topic. Since the release of GAO's 1986 studies of FDA's monitoring, discussion has been focused on proposals for providing the informational resources that would permit FDA to target more effectively its sampling of imported foods. In response to these concerns, the Omnibus Trade and Competitiveness Act of 1988 provisions that require FDA to develop a computerized summary of its sampling results and to enter into agreements with foreign governments to provide accurate pesticide-use information.

I believe, however, that even if these requirements are fully implemented, the sampling procedures used by FDA will remain a very serious impediment to the program's effectiveness. GAO estimates that FDA samples annually less than one percent of all imported food shipments. In 1987 FDA tested about 8000 of the roughly 1,000,000 imported food shipments, and found that about five percent of the tested shipments had violative levels of pesticide residues. (The actual rate is probably higher since FDA's multi-residue tests cannot detect residues of more than half of the total number of active ingredients used worldwide.)

Surprising as it may be, conversations with GAO and FDA officials indicate that findings from FDA's samples cannot be used to draw valid statistical inferences about the rate of violative residues for the population of all imported food shipments. If FDA's sampling program was so well-targeted that nearly all of the violative shipments in the total population were captured by their sampling, then we would not have to be concerned about the shipments that were not included in FDA's sample. However, since the adequacy of FDA's targeting program has been consistently questioned, and since the number of unsampled imported shipments is so large, knowledge of the rate of violations for the total population represents critical information about the extent to which FDA's monitoring program is protecting consumers.

The following hypothetical example of monitoring fruits and vegetables can be used to illustrate the potential seriousness of the sampling problem. Historically, fruit and vegetable shipments have comprised about seventy percent of FDA's sample. In 1987 according to the Agricultural Marketing Service, the U.S. imported about 310,000 twenty-ton shipments of fresh fruits and vegetables. If we deduct the 150,000 shipments of bananas, which rarely contain violative levels of residues that FDA can detect, we are left with a population of 160,000 shipments of imported fruits and vegetables that have a likelihood of containing violative residues. Assuming that FDA sampled 5500 imported fruit and vegetable shipments in 1987, the violation rate would have to have been no more than 0.20% for all violative residues to have been detected in FDA's 1987 sample. To the extent that the actual, but unknown, violation rate greatly exceeded 0.20%--and FDA's sample results suggest that this is likely--a very large number of unsampled shipments contained undetected violative residues and entered the commerical pipeline.

If the gap between detected and undetected violative shipments is in fact large, improved targeting through cooperative information-exchange agreements with foreign governments and increased computerization of sampling results may not be sufficient to close it. There is little reason to believe that information-exchange agreements can provide all of the necessary information on foreign pesticide-use. In many countries, the requisite information infrastructure simply does not exist and would be difficult to establish. Given the variety of pesticides available worldwide, the diversity of growing and shipping conditions within each country and across countries, and the continuous turnover of producers and exporters, the data on pesticide-use gathered through an information-exchange agreement would likely be far less than reliable. Even if that pesticide-use data was reliable, educated guesses would still have to be made in translating the data into a strategy for targeting violative shipments.

To address the potentially serious detection problems that may remain after the provisions of the Trade and Competitiveness Act have been implemented, the following measures should be incorporated into S. 722.

Shipper Certification of Pesticides or Labeling of Shipments. Certification or labels, when enforced with the threat of stiff penalties for inaccuracies, can provide more precise, more reliable and more timely information about pesticide-use than government information-exchange agreements. Both domestic and imported shipments should be required to be certified or labeled for pesticide-use. There is no reasonable economic or technical argument for exempting domestic shipments from these requirements. And, the inclusion of domestic shipments would preclude any claims that the monitoring scheme discriminates against imported foods.

Scientific Sampling Procedures Should be Required. At a minimum, FDA should be required to evaluate, in a rigorous manner, the performance of its targeting program. FDA could perform the evaluation by administering, at specified periodic intervals, scientifically designed samples of imported food shipments. The samples should be designed to enable FDA to draw statisically valid inferences about the rate of violations in the total population of imported shipments. If results of these samples show that FDA's current sampling procedure overlooks a substantial number of violative shipments, then FDA should periodically sample a much larger number of shipments in an effort to discover what kinds of violative shipments are not being included in its everyday sample.

Funding the Additional Monitoring. Residue Monitoring is crucial for the performance of the federal system that protects consumers from pesticide-residue hazards. To reflect this, a commitment of public funds should be made to cover the cost of the additional monitoring requirements. Since the recommended sampling procedures are fundamental and indispensable components of an effective monitoring system, they should be viewed as essential costs, not as marginal, discretionary expenses.

To help defray some of the costs of the additional samples, for example, importers (and domestic shippers) whose shipments are part of 'compliance' sampling of previous violators, can be charged fees equal to the cost of the compliance testing process. Since compliance tests in 1987 represented almost twenty percent of all sampled shipments, the amount of savings could be substantial. Moreover, the threat of having to pay for compliance sampling would serve as an added incentive to importers, domestic shippers, and both foreign and domestic producers to ensure that their shipments are not violative in the first place.

Statement of the
National Food Processors Association
Before the
Senate Labor and Human Resources Committee
on
S. 722
The Food Safety Amendments of 1989
June 15, 1989

NFPA is a national trade association representing approximately 600 companies, including food processors, and food packaging and equipment manufacturers. NFPA maintains and operates three research laboratories, employing over 100 scientific personnel, which conduct a wide range of food processing-related research, including pesticide residue studies and analyses. For many years, NFPA has recommended a detailed Pesticide Screen Program and provided other assistance to its members to help assure that processed foods do not contain illegal pesticide residues.

NFPA represents the vast majority of fruit and vegetable processors in the United States, including processors of many minor crops. Consequently, NFPA has a vital interest in pesticide tolerance legislation, and we support efforts to make available, consistent with public health, sufficient pesticides to maintain an adequate, wholesome and nutritious food supply.

Before addressing the specific legislation, I would like to stress several important points. First, our members are committed to undertake all reasonable efforts to assure that their products contain no illegal pesticide residues and that pesticide use is reduced to the maximum extent feasible, through Integrated Pest Management. Second, numerous studies conducted by our labs, the Federal Food and Drug Administration (FDA) and other government agencies have demonstrated that pesticide residues in processed foods are ordinarily far below tolerance levels and significantly reduced from levels contained in raw ingredients. Third, NFPA supports strong and effective pesticide tolerance laws and allocation of sufficient resources to permit the Environmental Protection Agency (EPA) and FDA to effectively implement and enforce those laws.

In the context of these principles, I would like to provide our perspective on H.R. 1725. As you know, this bill contains a complex and comprehensive revision of pesticide tolerance authority under section 408 of the Federal Food, Drug, and Cosmetic Law (FD&C Act). While we support several of the concepts embodied in the bill and agree that section 408 could be improved, we do not believe that a complete overhaul of the pesticide tolerance system is necessary or desirable.

This bill is complicated and raises many difficult issues of interpretation and implementation and is likely to impose unrealistic demands on EPA and the regulated industry. At a minimum, any tolerance reevaluation system should be coordinated and made consistent with the pesticide reregistration process mandated under the 1988 FIFRA Amendments. The three areas of the bill that concern us the most are: the elimination of benefits considerations in pesticide tolerance decisions, certain aspects of the required risk assessment methodology (e.g. that residues occur in 100 percent of commodities for which treatment is legal and at full tolerance levels), and the aggregate negligible risk standard.

Many of the bill's provisions would most directly impact pesticide producers and the EPA. These include data call-in requirements for active and inert ingredients, fee provisions, and timetables for data submissions and tolerance decisions. EPA and the pesticide producers are in the best position to evaluate whether these requirements are justified, and they both have expressed serious reservations about the bill.

NFPA fully supports reasonable requirements for reevaluation of existing pesticide tolerances. We are concerned, however, that the bill would impose regulatory demands that would precipitate the loss of valuable food use pesticides, especially for minor crops, through voluntary and automatic tolerance revocations that are not based on a determination of unreasonable risk.

In addition, there are two important issues that should be addressed in any pesticide tolerance legislation: the status of pipeline foods and national tolerance uniformity. We are gratified to see that the bill contains a pipeline provision, but we have a specific concern with respect to the language of that provision. Legally treated foods would only be exempt from tolerance revocation decisions where the dietary exposure to the food did not exceed a negligible risk. We believe that it would be more appropriate to provide that pipeline food could be sold in the normal course of trade unless the dietary risk posed by that food were significantly greater than negligible.

Pipeline foods are fully legal at the time of pesticide treatment, and growers and food processors ordinarily do not have access to pesticide toxicity data that would give them a reasonable basis for predicting a tolerance revocation action. Moreover, EPA would not be permitted to take into account the substantial losses to consumers and food processors if legally treated food were required to be destroyed. In light of these facts, and because pipeline foods ordinarily would be cleared from the channels of trade within 2 or 3 years, we do not believe that it is appropriate to apply the rigid and overly conservative negligible risk standard to pipeline foods.

The bill contains a provision that would authorize EPA to revoke a tolerance on an emergency basis where treated food poses a dietary risk that is "significantly greater than negligible." This is based on the premise that an ordinary tolerance revocation proceeding can take 2 or more years and that consumers should not be exposed during that period to treated food that poses significantly greater than a negligible risk. Because pipeline foods ordinarily are cleared from commerce within a period of time comparable to that required for completion of a tolerance revocation proceeding, the same safety standard should be applicable to pipeline foods.

The bill contains no tolerance uniformity provision. We believe this omission requires study. National pesticide tolerance uniformity is necessary to prevent erosion of effective federal food safety regulation and to avoid unreasonable burdens on interstate commerce. Where complete safety data is submitted in support of federal pesticide tolerances, as required under this bill, there is no reason to permit states to impose inconsistent tolerance requirements.

Against this background, I would like to address several specific aspects of the bill that are of particular importance to our members.

1. Negligible Risk.

The bill would establish a single negligible risk standard for pesticide tolerances on both raw and processed food. We strongly support this concept, which is consistent with recommendations contained in the 1987 National Academy of Sciences (NAS) report on regulating pesticide residues in food. We strongly oppose, however, two of the required exposure assumptions for determining negligible risk.

The bill would require EPA, in calculating dietary exposure with respect to a pesticide use, to assume, with narrow exceptions, that residues occur in 100 percent of commodities for which treatment is legal and at full tolerance levels. Studies have shown that these assumptions are inaccurate and result in exaggerated risk estimates. Pesticides are rarely used on 100 percent of crops for which treatment is legal. Pesticide residues on treated crops are almost always well below tolerance levels (and are often undetectable), and any detectable residues are further reduced during food processing operations.

The bill would permit EPA to calculate dietary exposure on the basis of the percentage of commodities actually containing residues only where it had reliable data with respect to such percentage and could show that "the national distribution of such percentage of such commodities . . . does not vary significantly from the distribution of the total amount of such commodities." In our view, this requirement for nationally uniform distribution is unnecessary and would be virtually impossible to satisfy.

EPA would be permitted to employ actual residue levels in exposure calculations only where it possessed reliable data with respect to such levels and lowered the tolerance to the level employed in the exposure calculations. The latter requirement would discourage the use of actual residue levels in exposure calculations. Tolerances must be set at a sufficiently high level to accommodate the maximum possible residues that can result from legal usage. Fixing a tolerance at actual residue levels, as required under the bill, is inconsistent with the fundamental concept of a tolerance.

2. Benefits.

The bill would eliminate any consideration of benefits in pesticide tolerance decisions. We strongly oppose this aspect of the bill. EPA is currently required, in making pesticide tolerance decisions, to give appropriate consideration to the necessity for the production of an adequate, wholesome and economical food supply. We believe that this provision is fully appropriate and should be retained. At a minimum, it is essential that EPA maintain authority to take into account the health benefits of pesticide uses, as well as the value to food companies and consumers of widely used pesticides for which there are no effective alternatives. The value to consumers is the continuance of a low cost abundant food supply.

EPA is required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to balance the risks and benefits of pesticide uses, and to consider the impact of its registration decisions on the production and prices of agricultural commodities. The proposed prohibition of consideration of benefits in pesticide tolerance decisions is fundamentally inconsistent with FIFRA and would nullify the benefits feature of FIFRA for all food use pesticides.

Food use pesticides have multiple important benefits that have long been recognized under FIFRA and the FD&C Act. Pesticides may be employed to prevent growth of harmful toxins in food. Pesticides help make available to consumers nutritious and healthful food, at affordable prices. Without effective pesticides, food availability would be reduced and prices increased. In addition, the Surgeon General and a National Academy of Sciences report strongly urged the consumption of fresh fruits and vegetables; an abundant and inexpensive supply of fruits and vegetables is possible because, in part, of the efficacy of agriculture chemicals. Pesticides enhance agricultural production and income, and provide support for the international competitiveness of United States food producers. Prohibition of benefits assessments in tolerance decisions would reverse a valuable and long-standing policy, and would ignore the important role of pesticides in United States agriculture.

Consideration of benefits in pesticide tolerance decisions is consistent with FDA's regulation of environmental contaminants in food. Under section 406 of the FD&C Act, FDA has authority to set tolerances or action levels for poisonous or deleterious substances that are required in the production of food or that cannot be avoided under good manufacturing practice. It is well established that FDA may take into account the benefits of food containing environmental contaminants, in terms of the likely economic losses from destruction or unavailability of that food, in fixing tolerances or action levels. Pursuant to this authority, FDA has set tolerances and action levels for a number of environmental contaminants in food, including polychlorinated biphenyls (PCB's) and aflatoxin, at levels in excess of a negligible risk on the basis of the substantial economic and food losses that would result from lower limits.

The required methodology in the bill for negligible risk determinations includes multiple conservative and worst case assumptions. In the light of these assumptions, the prescribed one in a million lifetime risk for pesticides which have no established toxicity threshold is equivalent to an extremely low, and in many cases nonexistent, actual risk. In these circumstances, it is appropriate for EPA to retain authority to take into account the benefits of pesticides that pose greater than a calculated negligible risk, especially where the pesticide is widely used and there is no effective alternative.

3. Reevaluation of Existing Tolerances.

The bill would require reevalution of all existing tolerances, including submission of supporting data, under strict time limits. EPA would be required to evaluate, within 90 days of enactment, all available safety data for each tolerance and exemption. Where EPA determined that there were insufficient data to make a safety evaluation, it would be required to request additional data within 30 days. The Agency would have only 90 days after receipt of the data to conclude its safety evaluation. Where EPA determined that a pesticide posed greater than a negligible risk, it would be required to take regulatory action to assure that each individual tolerance met the negligible risk test within two years and that the combined tolerances for each pesticide met the negligible risk test within four years.

These provisions are overly restrictive and are inconsistent with the 1988 FIFRA Amendments. The 1988 FIFRA Amendments contain carefully crafted requirements for reregistration of existing pesticides, including a full safety review, over a 9 year period, and food use pesticides have priority in the reregistration process. We see no need to duplicate or alter the existing reregistration process.

4. Aggregate Negligible Risk Standard.

The bill contains a new aggregate negligible risk test, which would go into effect six years after the date of enactment. At that time, the law would be amended to require that all pesticide tolerances for the same agricultural commodity have a combined negligible risk. EPA would have only one year to implement this requirement. It would not be feasible, employing current scientific knowledge and technology, to determine the interactive effects of multiple pesticide chemicals, and we are not aware of any food safety law that contains a similar requirement. Moreover, we are concerned that this requirement would be extremely difficult to administer and would impose unnecessary burdens on EPA in attempting to construct a rational basis for allocating risk among different pesticides used on the same crop.

5. Practical Method of Analysis.

Under the bill, EPA would be prohibited from establishing or leaving in effect a tolerance unless a practical method of analysis were specified by EPA, after consultation with FDA. A practical method of analysis would be defined as one that can be performed by FDA on a routine basis as part of surveillance and compliance sampling with available resources. EPA would be authorized to permit a nonpractical method only if it were not scientifically feasible to include the pesticide in a multiresidue method. Analytical methods for all existing tolerances would be required to be reviewed within 180 days of enactment, and all methods would be required to meet the practical analysis standard within 3 years.

There are a large number of important food use pesticides for which practical methods of analysis do not currently exist. There may also be developed safe and effective new pesticides for which there are no practical methods of analysis. We support the bill's attempt to encourage pesticide procedures that lead to development of practical analytical methods, and we agree that greater efforts should be made in this regard. It is very important, however, that any practical methods requirement not be so stringent as to cause the loss of pesticides for which multiresidue tests simply are not available.

Conclusion

We recognize that there is growing public concern over the safety of pesticide residues in food, and we are committed to assuring that food use pesticides are safe. We do not believe, however, that fundamental revisions in the pesticide tolerance law are necessary to accomplish this purpose. The 1988 FIFRA Amendments require accelerated reregistration of all food use pesticides. This important process should be given a chance to work.

We support codification of the NAS recommendation for a uniform negligible risk standard for pesticide residues in food, a proposal that EPA is implementing under current law. We also agree that the administrative procedures under section 408 should be streamlined and that provision should be made for greater public involvement in pesticide tolerance decisions.

Public confidence in pesticide safety must be achieved through effective consumer education which needs to be legislated, continued efforts to minimize pesticide use, the ongoing reregistration process and vigorous enforcement of existing law.

Dr. **Keith.** Mr. Gardner.

Mr. **Gardner.** Thank you. I am Sherwin Gardner, vice president for Science and Technology of the Grocery Manufacturers of America. I would like to thank the committee for the opportunity to participate in this hearing.

We have submitted an extensive statement for the record, and today I would like to focus comments on three aspects of the bill: pipeline provisions; the need for national uniformity for pesticide residue tolerances; and the need for flexible safety standards.

With regard to pipeline provisions, S. 722 does recognize the need to permit the continued marketing of foods which contain lawful residue levels prior to the modification of an existing tolerance, provided the food presents no more than a negligible risk to human health during the period it takes for the pipeline to clear. We understanding that in drafting the legislation, some pipeline provisions were omitted, but that these would be added to the legislation before it is reported to the Senate. With this understanding, we endorse those pipeline provisions.

With regard to national uniformity, unfortunately, this legislation still does not contain much-needed national uniformity provisions. We believe that any fundamental revision in the regulation of pesticide tolerances should be applied uniformly throughout every jurisdiction in the country. This bill would substantially expand the authority of EPA to regulate pesticide residues. It clearly provides that the setting of tolerances for pesticide residues would be conducted in an open and an efficient process providing an opportunity for all interested parties to fully participate. These provisions should permit States as well to participate effectively in the Federal tolerance-setting process.

Therefore, once a Federal pesticide residue determination has been made, that Federal standard should apply uniformly, unless it can be shown that due to dietary patterns or other factors peculiar to a particular State the Federal standard does not adequately protect the health of the citizens of that State. And as Commissioner Young noted earlier, good health has no boundaries.

With regard to the negligible risk standard, the bill utilizes a negligible risk standard as the basis for establishing safe residue levels of pesticides in foods. GMA agrees in principle with this approach, but we believe that the bill is unduly proscriptive in defining the negligible risk standard.

First, we do not believe that the bill should incorporate specific numerical standards since they become outdated by future scientific development. The Committee Report should indicate that under current regulatory practice and scientific standards, negligible risk for carcinogenic chemicals is a risk that does not exceed one in one million. Likewise, the report should indicate that under currently accepted scientific methodology, a 100 to one margin of safety is recognized as adequate for noncarcinogenic risks.

Second, we believe with respect to risk that the aggregate risk requirement of Section 6 of the bill is scientifically unsound and administratively unworkable. If the committee believes that this novel concept has merit, then the concept should first be studied and evaluated by EPA before enacted by statute. If appropriate, legislation could then adopt this form of risk assessment.

Third, with respect to risk assessment, we believe the inability of the EPA to consider health benefits is a significant defect in the statutory definition of negligible risk. For example, there are instances when there is a risk from certain naturally occurring carcinogens or other toxicants. That risk may be offset by the use of a pesticide to either prevent or reduce occurrence of the natural toxicant. Under this bill, however, the pesticide could not be employed even if the safety of the food supply would be improved by reducing the incidence of a riskier, naturally occurring toxicant. That condition should not be permitted to exist.

Finally, the bill appears to require that the same tolerance for both the raw commodity and the processed food be established at the residue level on the processed food that is actually considered by EPA in making its risk assessment. A tolerance at the as-consumed level for the commodity may be far lower than is achievable by the use of good agricultural practices. This would make the raw agricultural commodity unlawful for sale, notwithstanding the fact that subsequent processing would reduce those residues to a level that presents less than a negligible risk in the food as consumed. EPA needs flexibility to establish tolerance for the raw agricultural commodity at a higher level than that in the product as consumed when processing will reduce the level so that it presents no more than a significant risk.

Concluding our testimony, we can support S. 722 if it incorporates a national uniformity amendment and if it employs revised negligible risk provisions that are responsive to the substantive concerns outlined in our statement. We look forward to working with the committee to help develop the bill that addresses these concerns.

[The prepared statement of Mr. Gardner, along with responses to questions asked by Senator Kennedy, and additional materials submitted for the record follows:]

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PREPARED TESTIMONY OF
SHERWIN GARDNER
VICE PRESIDENT FOR SCIENCE AND TECHNOLOGY
GROCERY MANUFACTURERS OF AMERICA, INC.

Mr. Chairman and Members of the Committee on Labor and Human Resources, I am Sherwin Gardner, Vice President for Science and Technology of the Grocery Manufacturers of America, Inc. (GMA). GMA is an 80 year old national trade association comprised of over 130 companies which manufacture food and other products sold in retail grocery stores throughout the United States. GMA member companies employ over 2.3 million people nationwide and have annual sales in excess of $280 billion.

GMA has reviewed with great interest the provisions of S. 722, the Food Safety Amendments of 1989. This is a lengthy, detailed and complex bill. Although patterned after similar legislation introduced in the House of Representatives during the last Congress, S. 722 differs from its predecessor in a number of important respects. In GMA's judgment, some of these changes represent substantial improvement. Unfortunately, other changes raise serious questions in GMA's view concerning the workability of the legislation.

Section 408 of the Federal Food, Drug and Cosmetic Act (the FD&C Act) has provided strong assurance to the American public for more than thirty years that pesticide residues in or on food have not represented a significant risk to health. Notwithstanding this record of consumer protection, GMA agrees with the sponsors of S. 722 that improvements can be made in furtherance of this objective. Indeed, changes in science and technology since the enactment of Section 408 make it entirely appropriate for Congress to review and revise existing law to ensure continuation of a high standard of safety and to make the process of establishing residue tolerances more open, efficient and effective.

As previously indicated, S. 722 contains many complex and detailed provisions. S. 722 would make numerous, substantive changes in the procedures and the standards pursuant to which pesticide residue tolerances are established. With this in mind, GMA looks forward to working with Members of the Committee and its staff to address the technical questions which will undoubtedly arise as the hearings and markup of this complex legislation proceed. Today we wish to focus our comments on a limited number of substantive policy concerns that are of principal interest to GMA. Among these are --

- the pipeline provisions of S. 722;
- the need for national uniformity for pesticide residue tolerances; and
- the need for flexible safety standards.

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PIPELINE PROVISIONS

S. 722 recognizes the need to permit foods which contain lawful residue levels prior to the modification of an existing tolerance to continue to be lawful so long as the food presents no more than a negligible risk to human health during the period it takes for the pipeline to clear.

S. 722 also recognizes the need for a pipeline of flexible duration rather than one limited to a predetermined period. In some instances, the pipeline may clear in a matter of a few weeks. Such could be the case, for example, with some fresh and highly perishable foods such as fresh stawberries which enjoy a very limited growing season. On the other hand, the pipeline for other commodities must be significantly longer because of the standard industry practice by which such products are stored, processed and marketed. Commonly, products made from grains and cereals may not be marketed to the final consumer until three or four years following their harvest. S. 722 recognizes this fact and authorizes appropriate periods of delay to facilitate the clearing of foods in the pipeline consistent with sound industry practice.

In some instances, the revocation of a tolerance under S. 722 is the consequence of a lack of data rather than a substantive risk determination. Indeed, in those cases the tolerance is revoked precisely because of the inability to make a risk assessment determination. The legislation recognizes that in such cases foods already treated should be permitted to clear through the pipeline without requiring the Administrator to make a negligible risk determination, since the data on which such a determination would be based is not available. Rather than risk unwarranted disruptions in the Nation's food supply, the legislation takes the prudent and responsible approach of eliminating the tolerance prospectively.

We have reviewed the pipeline provisions in detail. We understand that a limited number of omissions may have been made in drafting the legislation. We hope that the omitted pipeline provisions will be added to the legislation before it is reported to the Senate. With this understanding, we support the pipeline provisions of S. 722.

NATIONAL UNIFORMITY

Unfortunately, the legislation does not contain much-needed national uniformity language. GMA believes that any fundamental revision in the regulation of pesticide tolerances should be applied uniformly throughout every jurisdiction in the country. This bill would substantially expand the authority of the EPA to regulate pesticide residues and includes authority to revoke tolerances or exemptions to protect public health. The bill clearly provides that the setting of tolerances for pesticide residues would be conducted in an open and efficient procedure providing opportunity for all interested parties to obtain information, evaluate safety data upon which tolerance determinations may be based, and fully participate in all aspects of the tolerance-setting process. These provisions should permit States to participate effectively in the Federal tolerance-setting process. Accordingly, once a Federal pesticide residue determination has been made, that Federal standard should apply uniformly unless it can be shown that due to dietary patterns or other factors peculiar to a particular State, the Federal standard does not adequately protect the health of the citizens of that State.

NEGLIGIBLE RISK STANDARD

The bill utilizes a negligible risk standard as the basis for establishing safe residue levels of pesticides in foods. This approach is consistent with advances in science and regulatory practice and is also consistent with the findings and recommendations of two National Academy of Science reports, one on risk assessment, issued in March 1983, and the other on regulating pesticide residues in food, issued in May 1987.

GMA agrees in principle with this approach. We believe, however, that the bill is unduly prescriptive in defining the negligible risk standard.

First, we do not believe that the bill should incorporate specific numerical standards such as the 1 in 1 million formulation for negligible risk and the 100 to 1 margin of safety standard for noncarcinogenic effects. The Committee Report should indicate that under current scientific standards, negligible risk for carcinogenic chemicals is a risk that does not exceed 1 in 1 million. Likewise, the Report should indicate that under currently accepted scientific methodology, a 100 to 1 margin of safety is recognized as adequate for noncarcinogenic risks. The bill should not, however, write these numerical standards into law since they may become antiquated by future scientific development.

There is no magic to the 100 to 1 margin of safety. That safety margin is currently employed in making risk assessment determinations in recognition of the limitations on the reliability of the underlying experimental data. Thus future improvements in the reliability of the underlying experimental data might warrant an adjustment in the margin of safety recognized as appropriate by scientists skilled in risk assessment. This legislation should not lock-in the limitations of 1989 technology by codifying a margin of safety driven by those limitations. The ultimate safety of the food supply might be better served by obtaining more reliable experimental data, even though that data would justify utilization of a margin of safety less than 100 to 1.

Conceptually the same is true for the 1 in 1 million negligible risk standard for carcinogens. The 1 in 1 million cancer risk, using conservative risk assessment assumptions, represents a statistical projection; it is not a prediction of actual future cancer experience. Indeed, because of the conservative assumptions employed in current risk assessment methodology, the actual level of cancer experience attributable to residues of a particular pesticide are virtually certain to be orders of magnitude less. The quantified level of statistical risk which is today viewed as "negligible" reflects the uncertainty in the underlying data employed in producing the risk assessment. Once again, future developments in test methodology and scientific procedures may result in substantially improved experimental data which could cause a theoretical statistical risk of more than 1 in 1 million to be viewed as "negligible."

We recommend that the bill not quantitatively define the acceptable levels of risk nor prescribe the precise methodology to be utilized. These determinations should be a function of the scientific methodology accepted at the time that the specific risk evaluations are made.

Second, we believe that the aggregate risk requirement of Section 6 of the bill is scientifically unsound and administratively unworkable. We do not believe that there is any current scientific basis for imposing an aggregate risk requirement. If the Committee believes this novel concept may have merit, the concept should first be studied and evaluated by EPA before it is mandated by statute. GMA recommends that the Committee require EPA to study the concept of aggregate risk assessment: (1) to determine whether there is any health benefit to be derived by imposing such a requirement; and (2) to ascertain the workability of an aggregate risk assessment requirement. Certainly there is adequate time for the EPA to conduct a thorough study of this issue and report back to the Congress. If appropriate, legislation could then be enacted requiring aggregate risk assessment. The Food Safety Amendments of 1989 would impose a host of new requirements on the EPA and result in a fundamental revision in regulation of pesticide residue tolerances. Obviously the Committee will need to engage in ongoing oversight of EPA's implementation of this statute. Thus, the opportunity will present itself for the Committee to consider whether to impose an aggregate risk requirement following receipt of EPA's study and recommendations on this matter.

Third, we believe the inability of the EPA to consider health benefits is a significant defect in the statutory definition of negligible risk. Consideration of "benefits" in establishing pesticide residue tolerances is a highly sensitive topic. Indeed the question has become so sensitive that the sponsors of S. 722 have completely rejected consideration of any benefits in performing a negligible risk assessment.

GMA believes that, at minimum, the legislation should permit consideration of health benefits in establishing permissible pesticide residue tolerances. For example, there are instances when the risk of certain naturally-occurring carcinogens is far greater than the carcinogenic risk presented by residues of pesticides used to prevent the formation of the naturally-occurring carginogen. If, however, the cancer risk posed by the residues of the pesticide used to prevent formation of the naturally-occurring carcinogen is greater than 1 in 1 million, under this bill the pesticide could not be employed despite the fact that the safety of the food supply would thereby be reduced through the increased incidence of the riskier, naturally-occurring carcinogen. If our true objective is the safety of the Nation's food supply this consequence cannot, and should not, be tolerated.

Finally, GMA is concerned that the legislation permits only a single tolerance to be established for both raw agricultural commodities and processed foods. There are instances in which residues of a pesticide on a raw agriculture commodity are significantly reduced during subsequent processing of the food, including washing, storing, and cooking. These processing activities ultimately result in a reduction in the residue level present in the food as consumed, whether raw or cooked. This actual residue level in the food as consumed may be employed by EPA in making a risk assessment. That risk assessment may indicate that the residue on the food as consumed presents a less than negligible risk. The bill appears to require that a single tolerance for both the raw commodity and the processed food be established at the level of the residues on the processed food actually considered by EPA in making its risk assessment. A tolerance at the as-consumed level for the raw agricultural commodity may be far lower than is achievable by the use of good agricultural practices. This would, in turn, render the raw agricultural commodity unlawful for sale, notwithstanding the fact that through sound industry practice in subsequent processing operations the residues would be reduced to a level which presents less than a negligible risk in the food as consumed. GMA believes that flexibility is needed in this regard to authorize EPA to establish a tolerance for raw agricultural commodities containing residues in excess of those that would exist on the processed food where the processing operations would reduce the residue levels so they would present no more than a negligible risk for consumption of the processed food.

CONCLUSION

In conclusion Mr. Chairman, GMA believes that S. 722 incorporates a number of important concepts that could advance the way in which pesticide residues in food are regulated.

We endorse the concepts embodied in the bill's existing pipeline provisions.

We urge the Committee to incorporate a national uniformity standard as part of this substantive revision of the Federal regulation of pesticide residues.

GMA continues to have substantial reservations regarding aspects of the negligible risk standard, however. While we agree in principle with the use of the negligible risk standard, we believe aspects of the definition employed in the bill are too prescriptive. We do not believe it wise for the Congress to lock into statutory language numerical risk assessment criteria which could be outmoded by future scientific developments. We believe it is unwise and premature to impose an aggregate risk requirement where that requirement has not been demonstrated to be scientifically warranted or administratively feasible. Further, in employing the negligible risk standard we believe that the legislation goes too far by precluding consideration of any benefits. We believe that the bill should not preclude EPA from considering health benefits. Finally, we believe flexibility is required to address circumstances where sound food processing practices result in a reduction of residue levels during processing.

GMA looks forward to working with the Committe to adopt a national uniformity amendment and to modify the negligible risk standard in the manner outlined above. GMA would endorse S. 722 if it incorporated a national uniformity amendment and employed revised negligible risk provisions responsive to the substantive concerns outlined above. We believe that a bill revised in this manner will preserve and enhance the safety of the American food supply and better serve the needs of both the food industry and the general public.

Thank you for inviting GMA to participate in this hearing.

RESPONSES OF SHERWIN GARDNER TO QUESTIONS ASKED BY SENATOR KENNEDY

1. The argument against aggregate risk assessment is based on the requirement in the bill that the sum of all residues of pesticide chemicals usually used on the same food would produce no more than a negligible risk of cancer. This requirement would take effect after completion of a six year process to assure that the residue of any single chemical on a food would produce no more than a negligible risk. Thus, the negligible risk safety standard would effectively be reduced still further, by orders of magnitude, and literally overnight.

First, this would appear to make all approved pesticide residue tolerances immediately illegal, and would begin anew a process of pesticide residue tolerance setting for all pesticides. This hardly seems a productive use of public and private resources.

Second, it is highly unlikely that residue tolerances could be reduced if the allowable amounts have to be apportioned among the several, indeed sometimes dozens of chemicals that are approved for use on a given commodity; this would be impractical and infeasible, e.g., if 10 pesticides are approved, the tolerance for each would become one tenth the level formerly allowed. Moreover, just because many pesticides may be approved for a given use does not mean that they all would be used. Regional differences in agricultural conditions coupled with weather and other environmental conditions would dictate which specific pesticides would be needed; there is no way to determine this in advance. Thus it is impossible to know how to apportion the allowances for residues in order to do the risk assessment, and it is far from clear that EPA would be able to implement implement this requirement.

Third, the notion of adding all cancer risks together and treating them alike is scientifically questionable; different chemicals affect different organs and have different outcomes. This concept at least merits further scientific study before being built into law.

Finally, carried to the extreme, the notion of aggregate risk could be applied to total dietary intake, as suggested by the question, so that the exposure to pesticide residues from consuming any and all fruits, vegetables, and grains would produce no more than a negligible risk. The effect of such a requirement would be to eliminate completely the use of pesticides for the reasons given above.

The objective of risk reduction from cancer and other illnesses associated with the results of tests on animals conducted with pesticide chemicals is not at issue, but the extent to which this objective is carried is the problem. Negligible risk, as defined in the bill, and as currently applied in regulatory practice, does indeed result in infinitesimally small risks to any individual. The standard of 1 in 1 million is an upper bound; it means that the probability is 95% that the risk is no larger than that and may in fact be zero. Further, the concept is one of risk and not certainty that any human cancer will result. In short, the concept of negligible risk as defined in the bill is a very conservative public health standard, and applies science to the greatest extent possible in an area still under study; aggregate risk is an inappropriate extension of current knowledge.

2. The use of Ethylene Oxide to fumigate spices in order to prevent bacterial contamination from insects and other naturally occurring field materials is the most common illustration of a health benefit provided by a pesticide. Such contamination can cause salmonella, a serious bacterial infection in humans. There are other naturally occurring toxins, such as aflatoxin in corn and nuts, and patulin in apples, that would be candidates for reduction or elimination through the use of pesticide chemicals. It is short-sighted to foreclose the possibility of reducing the risks from naturally occurring carcinogens if it can be scientifically demonstrated that the resulting overall risk, including that from the pesticide, is smaller than the risk without the pesticide.

3. The passage cited from the NAS 1987 report, taken in context, applies to the the different approaches now in force for raw agricultural products and processed foods: risk/benefit and zero-risk Delaney, respectively. The NAS recommended that a single negligible risk standard should be applied to both; GMA agrees with this principle.

The point we raised about flexibility in allowable levels of pesticide residues on raw agricultural commodities and processed foods is a different issue, and is neither in conflict with the NAS recommendation, nor with reduced usage of pesticides. The allowable residue level on a food as consumed must produce no more than a negligible risk. However, in order to achieve effective application of a pesticide on a raw agricultural commodity, higher residue levels may be necessary than will ultimately result when the food prepared from that commodity is consumed. Those higher levels are reduced in subsequent processing, storage and transportation stages to the no significant risk levels in the food as consumed.

The point GMA raises is not unfettered application of pesticides, but recognition that good agricultural practice will require a minimum application level in order that the pesticide work. That minimum level will always be higher than the level on a food as consumed. The provisions of S.722 need to reflect this.

4. The response to question 2. is applicable here also. The point GMA is making is one of a risk-risk trade-off, with the decision favoring the least risk outcome.

5. Mr. Chairman, GMA members are conscientious about the safety of the products they sell, most of which carry brand names that represent a significant resource that has taken years to develop. As a result, safety assurance is an essential consideration in their business operations. GMA members have installed extensive quality assurance systems to ensure that their products are safe and wholesome. Accordingly, pesticide analysis of ingredients and monitoring of suppliers are parts of these systems, which are designed to produce compliance with EPA and FDA pesticide residue requirements under current law.

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Statement of
the American Soybean Association
to the Senate Labor and Human Resources Committee

June 6, 1989

On

S. 722 — Food Safety Amendments of 1989

The American Soybean Association appreciates this opportunity to submit a statement for the record on S. 722, the Food Safety Amendments of 1989. ASA is a national nonprofit organization representing U.S. soybean farmers, which seeks to increase the opportunity for U.S. soybean farmer profitability through market development, research, government relations, and trade policy programs.

This statement on S. 722 is submitted not only on behalf of ASA but also for the Alabama Farmers Federation, the American Feed Industry Association, the National Cattlemen's Association, the National Grange, the National Pork Producers Council, the United Egg Association, United Egg Producers, and Women Involved in Farm Economics. These organizations represent a wide range of agriculture and agricultural products.

According to USDA, soybeans were the top cash income crop in 1988. In 1987, the most recent "normal" weather year, some 420,000 farmers produced 1.9 billion bushels of soybeans on 57 million acres, worth $11.8 billion. Almost half of the soybeans produced in the U.S. are consumed domestically and the remainder are exported. Exports of soybeans and soybean products, worth $7 billion last year, are vital to the United States balance of trade. The European Economic Community has traditionally been our largest regional market, and Japan buys more soybeans from U.S. farmers than any other single nation in the world. Other major foreign customers include Taiwan, the Soviet Union, South Korea and Mexico.

ASA members are familiar with the pesticides issues and are directly affected by the regulation of pesticides. In fact, ASA's Policies for the 1990's Task Force held 30 "listening sessions" across the soybean belt where farmers identified environmental policy as their number one concern. In general, soybean farmers support sound environmental production laws which balance their ability to economically use and conserve our natural resources.

ASA members apply pesticides to their crops, in their fields, to produce soybeans and soybean products that feed their families as well as many other families across the United States and internationally. Additionally, soybean products are the major protein source for livestock and poultry feeds and are becoming an increasingly important component of aquacultural feeds. As both users of pesticides and consumers of pesticide-treated products, our members have an appreciation for the great contribution these chemicals make to our food and fiber supply.

Approximately one billion pounds of pesticides are used annually in the United States. While a number of different pesticides are used on soybeans, herbicides are the most widely used. Soybean farmers need these pesticides to produce an abundance of soybeans safely and economically.

By definition, pesticides are toxic chemicals used as poisons against insects, fungi, weeds, and other pests. Some pesticides are used to enhance the appearance of a commodity and provide the high quality product that is expected by the American consumer. Other pesticides enable consumers to have a wide selection of produce all year long, and not merely during the growing season. Finally, pesticides are often needed to bolster nutritional food quality and safety. For example, some pesticides inhibit the growth of bacteria, a major food safety objective. In short, many of the achievements in the quality and quantity of agriculture products today may be attributed to the application of pesticides.

We are aware of the recent public alarm over the safety of the food supply and the particular concerns about pesticides that have been expressed in the media. As members of the agricultural community, we sympathize with these concerns. We believe, however, that this anxiety is truly unnecessary. Moreover, we are extremely concerned that some of our more frequently used pesticides may be precipitously removed from the market as a reaction to this crisis in confidence.

Contrary to recent press reports, existing evidence shows that our food supply is the safest in the world. Recent data from the Food and Drug Administration demonstrate that the overwhelming percentage of food contains no residues, and that most foods with residues are in compliance with established tolerance levels. There is no evidence that pesticides, when applied to food products in conformance with current regulatory standards, have caused illness or death in either children or adults.

Current risk assessment methodologies, which extrapolate animal toxicity data to human experience, are just that - estimates based on assumptions that a chemical, when fed to laboratory animals at high levels, will result in some comparable effect in humans. As a mathematical exercise, this may be appropriate. However, differences in factors such as dose, source of exposure, purity of the test material, the extent of tumor occurrence, and the size of the exposed groups must be considered. These factors are not sufficiently understood for anyone to state with certainty that pesticides which may cause cancer in animals will cause cancer in humans.

We commend the Committee for its efforts to review the law to guarantee the production of a safe, wholesome, and economical food supply. As currently drafted, however, we must oppose S. 722. We urge the Committee to consider carefully how certain changes in the law could have perhaps unintended and undesirable consequences.

Consistent Standards Should Benefit Consumers And Users

We agree with the fundamental premise underlying the Food Safety Amendments of 1989 that all pesticide chemicals, whether in raw agricultural commodities or in processed foods, should be regulated under the same standard of safety. In this regard, S. 722 provides that all food tolerances would be established under the same section of the Federal Food, Drug, and Cosmetic Act, and not under two different standards as under present law. Consumers should benefit from application of a uniform standard that is not dependent on the form of the food treated with the pesticide.

In 1987, the National Academy of Sciences, the preeminent scientific body, recommended that all pesticide residues be subject to consistent standards, whether in raw agricultural commodities or in processed foods, and whether covered by old or new tolerances. We applaud congressional efforts to implement this recommendation.

A Pesticide's Benefits Must Be Considered

As the bill is currently drafted, however, the benefits of a pesticide would not be considered in establishing a tolerance. Benefits to the consumers or to the food supply, the essential reasons for using the chemical at all, would not be taken into account in evaluating any risks from use of a particular pesticide. When a substance such as a pesticide has limited undesirable consequences as well as some desirable effect, both the risks and the benefits are relevant when determining whether such substance may be used and at what levels.

As earlier noted, pesticides provide numerous and varied benefits. Not only do pesticides help ensure the availability and affordability of agricultural products but they are often necessary to ensure the safety and nutritional value of many commodities. The health benefits offered by pesticides to the American consumer cannot be overlooked.

"Negligible Risk" Should Be More Clearly Defined

A further concern is that the negligible risk standard set forth in the bill is too complex and broad to meet the goals intended by the legislation. The concept of "negligible risk," or risks that are too small to be significant, is clearly appropriate in the area of pesticide regulation. However, as defined in S. 722, "negligible risk" for nonthreshold chemicals would be defined as not causing or contributing to a risk of any additional adverse health effect or an adverse health effect exceeding one in a million. For threshold risks, a margin of safety of at least 100 would be applied to a no observed effect level from animal studies to calculate an allowable human dietary level.

Additionally, the bill would provide that any adverse health effects be included in a negligible risk calculation. EPA would be required to use an overly cautious exposure estimate, and assume unrealistically that 100 percent of a food crop is treated with a particular pesticide at the tolerance level, unless other reliable data demonstrate otherwise. Finally, six years after enactment, the negligible risk standard would be applied based on the combined risk from the residue under consideration and all other residues having tolerances for the same crop.

Essentially, the net effect of the bill would be to read negligible risk as a zero risk standard - a standard not intended by the drafters of the bill. Indeed, an important reason to remove pesticide tolerances completely from reach of the Delaney Clause is to depart from a zero risk standard.

Available Alternatives To Currently Used Pesticides Must Be Considered

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires that pesticides, when used according to their label directions, perform their intended function without causing unreasonable adverse effects on man or the environment. That statute also requires that EPA consider the economic, social, and environmental costs and benefits of pesticides use in assessing whether a pesticide should be registered. EPA has already received direction to review the safety of pesticides' active ingredients registered prior to November 1, 1984, from the 1988 amendments to FIFRA (FIFRA '88).

Under FIFRA, EPA will not grant a registration for a pesticide unless all necessary food tolerances for residues have been established. As part of the reregistration requirements, EPA will reassess tolerances as the individual registrations come under review. Data required under FIFRA '88 includes residue data and an assessment of dietary risk.

Under S. 722, EPA would be given conflicting statutory charges. While FIFRA requires EPA to consider risks and benefits in granting a registration, S. 722 directs that only risks be considered. FIFRA '88 requires that priority in reregistration be given to pesticides that meet certain criteria (i.e., pesticides that are used in food and result in residues, pesticides that result in residues in groundwater, edible fish, or shellfish, pesticides that result in worker exposures, or pesticides with outstanding data requirements under the agency's regulations). S. 722, in contrast, would require that EPA complete within 90 days of enactment an evaluation of all existing safety data for each tolerance, determine whether exposure presents a greater than negligible risk, and initiate action to modify or revoke such a tolerance. If the deadlines imposed under S. 722 are intended to coincide, and not conflict with FIFRA '88, then we suggest that this be explicitly stated in the statutory language of S. 722, and not left to interpretation by the agency.

As drafted, EPA would be forced to divert its already scarce resources toward tolerance review, away from the previously mandated reregistration process. Registrants would be forced to evaluate, during both the tolerance and reregistration processes, whether to pursue continued regulatory approvals for a pesticide chemical. Any mandatory reevaluation of tolerances under S.722 thus constitutes, at best, an unnecessary and redundant regulatory burden. The resulting regulatory burden on an agency already criticized for not meeting its existing deadlines tends to negate any realistic or additional contribution from the legislation.

Should FIFRA '88 not be adequate to ensure expeditious pesticide review, minor amendments to EPA's existing statutory authority, not a full scale proposal in a different statute, should be proposed. This could include, for example, specific authorization for EPA to reevaluate tolerances and require reregistration of post-1984 pesticide registrations.

Summary

S. 722 is significant since it would require evaluation of all pesticide residues under the same risk standard, regardless of the form of the food in which they might be found. This addresses the primary concern of preeminent authorities (such as the National Academy of Science) that pesticides, whether marketed in raw or processed foods or under new or old tolerances, should be governed by consistent standards. Application of the very stringent negligible risk standard proposed, however, would effectively subject all food products to a zero risk standard which ironically is what the bill is designed to replace. Finally, and perhaps most importantly, the numerous benefits of pesticides must be recognized, and reasonable risks accepted.

Our food supply is safe, wholesome, and economical. Much of the credit in providing the safest and most abundant food supply in the world can be attributed to pesticides. Our attention should be focused on controlling those health risks that are real, while fostering the continued availability of beneficial substances. The American Soybean Association stands ready to assist the Committee in addressing these real concerns.

Thank you for providing us with the opportunity to submit a statement on this legislation.

WRITTEN STATEMENT OF THE
NATIONAL AGRICULTURAL CHEMICALS ASSOCIATION
BEFORE THE
U.S. SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

JUNE 6, 1989

Thank you for the opportunity to submit these written comments on S. 722, the "Food Safety Amendments of 1989."

We appreciate the efforts in S. 722 to address the recommendations of the National Academy of Sciences on the Delaney paradox. We know the sponsors of S. 722 worked hard to solve the problem the Academy identified and problems seen by others elsewhere. However, S. 722 goes well beyond what is needed. In fact, it would be difficult for us today to suggest amendments to fix the bill the way it should be fixed. Accordingly and after close examination of the bill, we must oppose S. 722. We suggest a new start with a bill that may be more sensitive to broader public policy issues, grounded in science, and attainable.

Several flaws of S. 722 in this regard are notable:

- the major adverse effects of the bill on food production;

- the numerous inconsistencies between the bill and current law and practice;
- the failure to consider pesticide benefits;
- the un-achievable deadlines;
- the confusing, rigid and extreme assumptions in risk assessment; and
- the misguided regulation of all inert ingredients.

There are others. This Committee no doubt has and will be hearing a great deal more on these issues. In this respect, we share these concerns and amplify on them later in this written statement.

There are also larger policy issues:

First: What food quality standards should we have? Congress has answered that question in the current FFDCA law: it must be safe. S. 722 changes this standard to a new and expansive "negligible risk standard." While the National Academy of Sciences said a negligible risk standard should replace the archaic Delaney Clause for carcinogens--a proposal we endorse--S. 722 expands and changes the concept. S. 722 uses the same expression, but defines it differently and applies it to carcinogens and non-carcinogens alike.

Second: How do we balance certainty in setting public policy with agency discretion and scientific progress? A difficult question, one we believe is not answered in the encumbering procedures and forced assumptions of S. 722. We must distinguish beneficial clarity from excessive detail.

Third: How do we make sure we have enough high quality and inexpensive food? S. 722 doesn't acknowledge this concern. Pesticides provide unquestioned benefits to the public through an abundant, healthful, inexpensive and varied supply of food. Common sense and sound public policy demand that pesticide risks and benefits be considered together.

Fourth and finally: How can we have a fair and open process in resolving food quality issues? Just as Congress seeks the truth through hearings--where Members can look someone in the eye, ask tough questions, and then make up their minds--EPA should do the same on tolerances. The process for setting and revoking tolerances in S. 722, which calls for hearings after-the-fact, will only lead to public frustration and a sense of injustice.

NACA wants to assure this Committee that the agricultural chemicals industry will assist it and this Congress in preparing and passing legislation to amend the Delaney Clause and to do what we can to responsibly provide an abundant and healthful food supply. In the remainder of this written statement we will address in detail a number of problems raised in S. 722.

Negligible Risk Standard

S. 722 would replace existing FFDCA standards for tolerance-setting with a new "negligible risk standard" applicable to both raw and processed food. While clearly an improvement over the zero-risk approach of the Delaney Clause for carcinogens, the new concept is misapplied and unworkable.

A panel of the National Academy of Sciences observed in the recent report, Regulating Pesticides in Foods: The Delaney

Paradox, that the strict requirements of the Delaney Clause actually interfere with measures to reduce cancer risks, and block safer product introduction, and recommended that it be replaced by a "de minimus" or "negligible risk" standard. Using the NAS recommendation as a departure point, S. 722 then redefines the concept and applies it to all risks, both carcinogens and non-carcinogens. The amendment's deviation is particularly curious, since neither the NAS nor many others have criticized the FFDCA standard for setting tolerances except for the Delaney Clause.

Also at variance with the NAS recommendation, the bill defines "negligible risk" for non-threshold risks as one-in-one-million or 10^{-6}. We have found no federal or state statute numerically defining "negligible risk" as the bill does. Indeed, the NAS report said views on negligible risk vary widely. The Executive Director of the NAS Board on Agriculture, responsible for the NAS Report, recently testified before a House Agriculture Subcommittee as follows:

> The NAS committee discussed at virtually every meeting whether to recommend a quantitative benchmark for negligible risk as part of its definition of this important concept. The committee was both sensitive to and well aware of valid arguments both for and against specifying a quantitative benchmark in the definition of negligible risk. In the end, the committee was persuaded that quantitative risk assessment methods, and the science underlying estimates of oncogenic risks, were too fragile and changeable to either assert that risks below a certain level are truly "negligible," or that risks above the "negligible" level indeed pose a significant risk of cancer in man. Such judgments, in the committee's view, can only be made on a case-by-case basis following a thorough review of the complete toxicological database available on a particular chemical. Even then, such judgments may be very hard to make.

This reluctance to set numerical values for negligible risk is prudent and understandable. Knowledge is rapidly advancing in the science bearing on risk assessment, and society needs the flexibility to modify its perception as conditions change, and views of acceptable risk and ways to measure it mature.

Negligible risk is also defined in S. 722 as one hundred times less than the "no observable effect level" or "NOEL" for threshold risks. The NOEL is the level of exposure which reliable experimental data, derived from exposing animals to the pesticide, shows no adverse effects in the experimental animals. Although a 100 fold safety factor is typical in EPA practice, there are instances where flexibility is both appropriate and fully protective of the public health. A 10 fold safety factor has long been recognized as adequate for cholinesterase inhibiting substances.

The application of a 10^{-6} negligible risk to all non-threshold effects is especially troubling. Since the definition is not limited to just carcinogens, it is unclear what effect this new and highly restrictive standard will have. We are not even sure what would be covered by the "non-threshold" category, other than carcinogens. An understanding of non-threshold risks posed by non-pesticides, subject to the same precedent under the same or other laws, is even more problematical.

Additionally, the bill is ambiguous in other aspects of the negligible risk definition. The bill requires that the lifetime exposure not be "likely to cause or contribute to any additional adverse human health effects." This provision suggests that, while negligible risk may be estimated at 10^{-6}, in addition there must not be likely any additional non-threshold effects in the U.S. population at any level. It appears that the bill permits a negligible risk, only to say that no risk is acceptable.

Finally, S. 722 calls for the use of "conservative" risk assessment models in determining negligible risk. Conservative mathematical risk assessment models are not necessarily the most accurate models. The models used should be those which best fit the animal data and will vary from product to product. The law should be flexible enough to allow for future advancements in the accuracy of models as they become available and pass the test of appropriate scientific peer review.

Elimination of Benefits Consideration

EPA is currently required to consider both the risks and benefits of pesticide use in registering pesticides under FIFRA and in granting raw commodity tolerances under FFDCA. Only the Delaney Clause implicitly prohibits consideration of pesticide benefits. S. 722, however, eliminates all consideration of pesticide benefits in setting tolerances. Rather than resolving inconsistencies between the two statutes prompted by the Delaney Clause, the amendments actually make the inconsistency more unworkable. A pesticide may be granted a FIFRA registration because the benefits of pesticide use outweigh its risks, yet fail to receive a tolerance because its risks exceed the negligible risk standard. The stark reality presented by S. 722 is that a pesticide could be lawfully used under FIFRA, but the treated produce be illegal under FFDCA.

The amendments have an even more basic failing. Consideration of pesticide benefits, along with their risks, is good public policy and an appropriate standard for making regulatory decisions on pesticides. In the context of FFDCA, decisions on permissable pesticide residues are directly related to the ability of agriculture to provide inexpensive and quality food, and to the ability of others to provide clean and healthy eating, working, and living conditions.

The benefits of pesticides in assuring a safe and abundant food supply are numerous. For example:

- Pesticides provide a strategic resource in the battle to control pests that will otherwise cause widespread and significant damage to almost all crops grown in the United States. Pesticides lead to increased availability, lower prices, and improved quality of commodities, especially fruits and vegetables. The attractiveness, nutrition and availability of good food is an invaluable benefit to the public.

- The benefits of pesticide use are derived directly from the control of insects, nematodes, weeds, rodents, and plant pathogens. In the pest management context, insecticides are the only practical control measure for insect pest populations approaching or at infestation levels that will cause major crop damage or health risks. They have rapid curative action, offer a wide range of properties, uses, and methods of application to pest situations, are low in cost, and are associated with substantial labor savings to growers and benefits to consumers.

These facts, as compelling as they might be, mask the potentially devastating regional and individual crop impacts due to the loss of chemical pesticide control. In many areas and on many crops, pesticides are the only means to control pests whose presence would otherwise prohibit production of certain crops. Without these tools to produce crops, many individual farms may fail.

Finally, we would like to dispel the notion that there is no regulatory system or guidelines for analyzing the benefits of pesticides. In a recent report on a study commissioned by the U.S. Department of Agriculture, entitled "Agricultural Benefits Derived from Pesticide Use: A Study of the Assessment Process," the project director and author of the report notes:

> Nowhere in the world is there a pesticide data gathering system as impressive or comprehensive as the United States Department of Agriculture/National Agricultural Pesticide Impact Assessment Program (USDA/NAPIAP). The quality and amount of pesticide information available from the system is phenomenal.

The report goes on to describe the process and presents recommendations for improvements.

The EPA also has guidelines for benefits analyses. They were first published in May 1980, later revised in September 1986, and again in March 1988. These guidelines address more than just economic impact to the pesticide user (the farmer). They direct EPA staff to evaluate integrated pest management, consumer impacts, social and community impacts, among other factors. We acknowledge that improvements may be made. However, to totally disregard benefits or for others to suggest that no structure or process is in place is wrong.

EXPOSURE ASSUMPTIONS

The risk posed by a substance depends both on its affects and exposure to it. In essence, no exposure means no risk.

S. 722 not only assumes that there is always exposure to a pesticide--a bold assumption in fact--but assumes the most extreme case. In calculating exposure to a pesticide, the bill requires EPA to make the following assumptions and considerations:

- All authorized crops have been treated,
- All crops have their maximum permitted residue,
- The residues are consumed for a life-time,
- All other dietary exposures, including drinking water, are included,
- All other ways of exposure must be considered,
- All chemically or pharmacologically related substances must be considered,
- Consumption by the most sensitive population group,
- Consumption by the group with special food consumption patterns, and
- Consumption by the group that eats the greatest amount of treated food.

Even for those with little knowledge of pesticide risks, these assumptions are readily seen as impossible. Yet, the bill requires EPA to set tolerances based on these rigid and extreme assumptions.

To blunt criticism of its unreasonable exposure calculation, however, S. 722 contains a narrow exception to permit use of actual exposure data. The exception is problematic. First, if such data were used, the tolerance must be set and presumably enforced at the level used in the exposure assessment, such as residues on food in the store, rather than at the farm gate as it is done now. Even setting aside its disruption, enforcement in the supermarket would fail to adequately monitor pesticides used at the source and to stop further distribution of foods that exceed the tolerance. Second, the exception itself calls for information about actual use that is unlikely to exist. For example, the bill calls for information on the percent of raw agricultural commodities or processed foods in which the pesticide chemical occurs and national uniformity in distribution of such food. Given wide disparity in pests, pesticide usage, and marketing of agricultural commodities, it would seem that few foods with residues are distributed evenly throughout the population. In short, S. 722 offers a "no-exception exception."

Inert Ingredient Tolerance Requirements

S. 722 poses a simplistic solution to a complex issue. If enacted, the results of the amendments will be confusion in how inerts are regulated, disruption, and significant resource impacts, with little or no benefits to food safety.

Under S. 722, the only permissible inerts would be those that are "generally recognized as safe" ("GRAS"), or essential to the active ingredient, or scientifically impossible to replace with GRAS substances. Accordingly, the bill requires EPA and registrants to sort through an existing inventory of 600 inerts, including many already determined to be GRAS or exempt from tolerances, to reassess their status and obtain tolerances if required. Given that there are only 300 food use active ingredients, the bill thus triples EPA's administrative burden. EPA correctly points out in its testimony that it will face the prospect of reviewing thousands of new toxicity studies, a deluge of new tolerance petitions, and thousands of new tolerance amendments as formulations must be modified. Unlike other statutes and other provisions of S. 722, moreover, the inerts provision sets no priorities and allows little or no transition from current law and practice. The result will be chaos.

The bill's inerts provision would also impose substantial and unfair testing requirements on pesticide producers, with little or no overall improvement on public health. Inert ingredients in pesticides are the same substances used in much larger quantities throughout American industry as solvents, surfactants, preservatives, carriers and for other uses. Their use in pesticides and resulting public exposure is minuscule by comparison. Yet, S. 722 saddles pesticide producers, including many small businesses, with full testing requirements necessary for tolerance setting. In doing so, the bill ignores the broader equities for such tests set out in the Toxic Substances Control Act that was intended to regulate such industrial chemicals. The result of S. 722 will be either an unfair assessment of testing responsibilities on the agrichemical industry, or the abandonment of many valuable inerts--not because they are unsafe--but because of the high cost of tests appropriate to food residue considerations.

In summary, the bill would require tolerances for all inerts--regardless of how much theoretically could be present or the toxicity. We acknowledge that risks associated with inerts need to be managed. However, a "threshold of regulation" concept and establishment of priorities is a more sensible and realistic approach. We submit that the EPA policy published in the Federal Register on April 22, 1987, is such a sensible and realistic approach.

Practical Methods of Analysis

S. 722 begins with a good concept, that FDA should have the necessary analytical tools to be able to enforce the law, and turns it into a bad one. The bill requires testing methods for pesticide residues (including inerts) that can be conducted in "routine" surveillance and compliance sampling.

Failure to have such a method may result in tolerance revocation or a bi-annual review to determine whether the method is "not scientifically feasible." Apparently, in this latter respect, technical feasibility, not cost or personnel qualifications, is the only consideration.

Current FFDCA requires a pesticide registrant to provide an analytical method suitable for enforcement of a tolerance. This method is submitted to the agency which, in turn, conducts trials to prove the method's utility prior to granting the tolerance.

The meaning and affect of the bill's monitoring provisions are not clear. The provisions have been widely interpreted to require use of as yet undiscovered multi- and single-residue analytical techniques. While certainly the objective may be desirable, to develop and make available methods for FDA surveillance, the punitive thrust of the provisions is not. In essence, S. 722 holds deficient tolerances in perpetual hostage until there is a scientific breakthrough. While pesticide innovators may want to develop multiresidue and other tests to facilitate FDA monitoring, the new technology may be discovered only in the distant future or, when available, be prohibitively costly.

Finally, S. 722 simply seems to miss the point that all residues do not need to be routinely monitored. Even setting aside the administrative burden on FDA to conduct such universal surveillance, the usage patterns of pesticides and other factors do not require it. For example, it would be pointless to routinely monitor for substances where there is no reasonable expectation for residues and a tolerance is set at the sensitivity of the analytical method. This is the case for many pesticides--especially for non-systemic and/or rapidly degraded compounds which are applied at planting and the crop is harvested 3-4 months later. We acknowledge there is room for improvement in the scope of the pesticide residue surveillance system. However, it makes no sense to have a goal that everything needs to be monitored routinely.

Accelerated Reevaluation of Existing Tolerances

With the objective of expediting review of existing tolerances, the bill requires EPA to meet totally unrealistic deadlines. For example, within 90 days of the bill's enactment, the agency must review all data supporting thousands of tolerances to determine whether there is "reason to believe" the new negligible risk standard is met or exceeded for each tolerance. Also, if data is insufficient to make such an evaluation, EPA must require the additional data within 30 days and have 90 days from receipt to evaluate it.

The bill fails on an even more basic level. S. 722 does not even acknowledge the 1988 FIFRA amendments that set out an ambitious schedule for pesticide reregistration. EPA's work on reevaluating scientific data for all food use pesticides and reconsidering existing tolerances as part of reregistration is well underway. No new legislation is needed to accomplish this task. The agency is now in the middle of a comprehensive reassessment of tolerances on schedule and should be completed for food use pesticides in under nine years. At best, the bill's deadlines and detailed provisions on tolerance reconsiderations are redundant. At worse, S. 722 will conflict with the Congressional mandate in recent FIFRA amendments, delay good work in progress, and substantially increase the cost and complexity of an already demanding administrative effort.

Aggregate Negligible Risk Standard

Six years from enactment, S. 722 would require yet another change in the standard for setting tolerances. Beginning then, to be completed in one year, the tolerances for all pesticides "usually used" on an agricultural commodity must meet the negligible risk standard in aggregate. This novel concept is extraordinary in scientific and administrative complexity.

Aside from the impractical deadline of one year to review and act on all tolerances under the new standard, it is unclear what pesticides and what risks must be aggregated. The term "usually used" has no current definition in regulation or practice. Combining different risks into a single negligible risk assessment, moreover, is conceptually, if not scientifically problematic. Finally, no fair and simple means is evident to allocate risks among competing pesticides on the same commodity. If the negligible risk "quota" is filled by a pesticide to control weeds, it is difficult to see the justification for barring use of a pesticide necessary to save the crop from insects. This "quota" is particularly problematical for the introduction of new and safer pesticides when negligible risk is met by existing pesticides.

Perhaps on a more fundamental level, it is by no means certain that such draconian measures will reap any public benefits. If "negligible risk" means that the risk posed by a pesticide residue is insignificant, the thought of aggregating the risk of several such insignificant residues is more an intellectual curiosity than a real concern. If anything is clear, in light of the aggregation of extreme safety factors and conservative assumptions in setting tolerances in the first place, this final aggregation of all tolerances on a commodity shows that S. 722 is seriously flawed.

Data Call-In

In view of the many complexities and potential for statutory conflicts that it introduces, it is a mystery why S. 722 grants EPA data call-in authority under FFDCA. This is especially true since EPA has broad existing authority to require the same data under FIFRA.

Scattered throughout the bill, S. 722 gives sweeping powers to require new health and safety data to support tolerances. Similar to FIFRA, there are few limits on the type and quantity of testing requirements. Unlike FIFRA, however, any failure to submit the data on time (except for "extraordinary circumstances") will result in automatic tolerance revocation. Also, unlike FIFRA, a hearing on the merits of the data call-in and deadlines would be available only after the tolerance is revoked. Since the cost of data development and potential for legitimate controversy are so great, S. 722 goes too far in granting EPA both the authority to require data and the procedural hammer to argue the equity and lawfulness of its demand after-the-fact.

Data Compensation

One of the problems presented by S. 722's data call-in authority is the bill's failure to recognize a data submitter's property rights in its data. Ironically, the same data submitted under FIFRA or TSCA would not be protected under FFDCA by a data compensation provision. Data compensation refers to the amount one company must pay another for the use of its research and test data. It is based on the equitable principle that certain companies have risked significant up front investments in the research and development of new products and that such companies be permitted to ask follow on registrants or others who wish to use the data to share part of the financial burden.

In the past, the issue of data compensation for pesticide tolerances has been absent under FFDCA, since data submitted for tolerances have been supplied to EPA under the protection of FIFRA. S. 722 now proposes an independent authority for data submissions under FFDCA without the same provision for data compensation. Aside from failing to recognize the inequities of such omission, this difference may lead to the incongruous result that data submitted under FIFRA for a registration would receive compensation, while the same data for a tolerance under FFDCA would not. While no one suggests double payment for the same data, FFDCA should work together with FIFRA and TSCA to ensure their respective procedures and policy judgments are preserved.

Confidentiality

S. 722 also fails to adequately protect confidential information from public disclosure, both before and after EPA acts on a tolerance or exemption. Again, FIFRA has detailed provisions on public access to data, allowing full disclosure to non-competitors of health and safety data supporting registrations. Data call-in and residue monitoring provisions for inert ingredients under S. 722 would provide no such protection. There is no justification for such disclosure of confidential business information to competitors, let alone the creation of troubling conflicts between the two laws.

Equally troubling is the bill's provision to allow pretolerance disclosure of data supporting a petition. "Cherry picked" from a package of FIFRA amendments negotiated in 1986, the bill now presses one side of the compromise in isolation. Even apart from this equitable consideration now, as it did in

1986 this preview of data raises troubling issues in property rights and in the government's role in protecting the public interest.

Procedures for Setting and Revoking Tolerances

The requirements for setting, modifying and revoking tolerances described in Section 408(d) of the amendments constitute the worst possible combination of administrative procedures. The bill introduces to FFDCA the delays and imprecision of notice-and-comment rulemaking, then complicates the new procedures with an after-the-fact adjudicatory hearing. The result will be duplication and delay an acting on tolerances, with public frustration and sense of injustice.

The bill allows EPA, on its initiative, or any person to petition EPA to issue, modify, or revoke a tolerance or exemption. The action is subject to a notice-and-comment rulemaking not now contained in Sections 408 and 409. Such informal rulemaking, while praised for its speed and alleged openness, suffers from a lack of agency accountability, indifferent rulemaking records, and arbitrary results. Compared with formal adjudicatory hearings before an impartial examiner, where anyone may participate and properly develop the record for agency action, informal rulemakings are a poor second choice. S. 722, however, combines both procedures, thereby allowing final agency action on a haphazard informal rulemaking record and then forcing the public to go through an after-the-fact formal hearing to challenge the agency's decision. Only after this needless delay may the public seek judicial review.

Finally, the bill fails to make any provision or even acknowledge the parallel requirements in FIFRA for pesticide registration. FIFRA and current FFDCA procedures work in tandem to allow EPA to address registrations and tolerances together. The processes are sufficiently alike to allow EPA to grant and revoke tolerances and registrations without having to pursue distinctively different procedures or to develop separate records to support its actions. S. 722 introduces new and incompatible procedures. While EPA may act on a registration without rulemaking under FIFRA; it must conduct a rulemaking under S. 722 to set a tolerance. While EPA may cancel a registration under FIFRA through an adjudicatory hearing; it must revoke a tolerance through rulemaking, followed on request by an adjudicatory hearing under S. 722. While different procedures in different statutes are not in themselves a fatal flaw, in this instance --where orderly and expeditious action on a single pesticide is important--it makes absolutely no sense.

Judicial Review

S. 722 contains a major deficiency in its judicial review provisions. Making objections and requesting hearings would not be required as prerequisite to obtaining judicial review of a denial of a petition. In fact, a person whose petition was denied would not even be entitled to file objections or request a hearing. This provision seems designed expressly to overrule Nader v. EPA, a recent federal court decision saying that environmental groups could not obtain court review of EPA's informal denial of their petition to revoke a Section 409 tolerance until objections to the denial had been filed and EPA had an opportunity to rule formally on the objection. Other provisions of S. 722 would provide citizen groups with grounds to petition for revocations of tolerances and exemptions; this provision would allow the groups to proceed directly to court upon initial EPA denial of such a petition.

It is difficult to see why the issuance, amendment, or revocation of tolerances should be judicially challengeable only after both informal and formal rulemaking, while petition denials could be the subject of direct judicial review without any opportunity for development of an administrative record or consideration of the views of other interested persons under either informal or formal rulemaking.

Expiration Dates

Presumably in the interest of giving EPA greater authority over termination of tolerances, S. 722 proposes to grant EPA authority to establish expiration dates. This is an error both in procedure and public policy.

The operation of an expiration date is effectively to "revoke" a tolerance in the future without a hearing or other due process. S. 722 fails even to provide at expiration of the tolerance its minimal procedures of notice-and-comment rulemaking or after-the-fact hearing. There is no suggestion either in the bill that the "expiration date" is contingent on the future submission of data, such as might be the case for conditional registrations or conditional tolerances. Finally, there is no effort to coordinate this draconian measure with FIFRA's registration procedures that have no such provision. In short, "expiration dates" undermine the procedural rights described in the bill and present in current law for fair and orderly revocation of tolerances.

Expiration dates for tolerances also strike at the incentives of crop protection research and development, as it would for most other high investment industries under similar circumstances. Pesticide producers invest millions of dollars to discover, develop and market new crop protection chemicals. S. 722 proposes to place a time limit on recovery of that investment. This "drop dead" or expiration date will have the effect either of raising product prices to permit capital recovery within the time alloted, or of forcing responsible companies to seek less speculative enterprises elsewhere.

Pipeline Provision

Scattered throughout S. 722 are pipeline provisions that would permit foods in commerce to be consumed, after a tolerance is revoked or lowered, if the pesticide residue meets the old tolerance and does not exceed negligible risk. The obvious threshold failing of the provision is that it does not cover unharvested crops. Since most pesticides are applied during the growing season, the pipeline provision does little to protect farmers and the food processors who contract with them, when pesticides are lawfully used in accordance with the label and tolerances are later changed.

Again, on a more basic level, the bill fails to coordinate with similar pipeline provisions of FIFRA. FIFRA authorizes EPA, upon the cancellation of a product and within EPA's discretion, to allow pesticides to be used until supplies are exhausted, on the assumption that limited use over the country is environmentally preferable to concentration of the product in stopping its use and ordering disposal. S. 722 undercuts this sound environmental policy by effectively prohibiting use of all unapplied pesticides in storage and inventory. In limiting the pipeline provision to only harvested crops, S. 722 not only makes sale of treated and growing crops potentially illegal, but also makes a farmer's pesticide stock and all inventory upstream worthless and unusable, even if use is environmentally preferable.

Imminent Hazard Provision

S. 722's imminent hazard provision suffers from vagueness and inconsistency with FIFRA. The amendments authorize EPA to revoke or modify tolerances or exceptions without prior notice and comment, and without a hearing, if the agency finds a risk "significantly greater than the negligible risk standard." Considering that negligible risk is established at virtually zero, it is problematic what level would constitute "significantly greater" than next to nothing. Also, notably, the determination of imminent hazard suggests no consideration of the immediacy of the risk or whether there is, in fact, a risk to human health. Imminent hazard in the bill appears to be merely a quasi-mathematical analysis of how much greater than negligible risk is "significant."

The bill also neglects to coordinate its "imminent hazard" authority with similar "suspension" authority in FIFRA. Again, as with other sections of S. 722, where actions may be permitted or denied under the amendments in direct conflict with other statutory authority, an imminent hazard may be found under S. 722 and not under FIFRA, or the reverse. As previously stated, S. 722 authorizes emergency action if EPA finds a risk significantly in excess of negligible risk. In contrast, FIFRA grants such authority when the continued use of a pesticide during the time required for a cancellation hearing would likely result in "unreasonable adverse affects on the environment." The FIFRA concept is based on both an urgency of action and ultimate risk-benefit analysis. S. 722 is based on neither.

User Fees

The amendment requires EPA to collect user fees to cover the cost of implementing the amended Section 408. It is unclear what impact the fee will have in light of the dramatic increase in costs imposed by S. 722, the ongoing affects of over $150 million in reregistration fees contained in the 1988 FIFRA amendments, and the authority now in FFDCA to impose fees. However, many in agriculture and elsewhere have grave reservations about agency programs and congressional initiatives employing user fees to raise revenue for government services. The concerns are threefold.

First, the public, and not the pesticide industry or users, is the main beneficiary of food quality regulation. User fee advocates argue that the pesticide industry and its customers derive a benefit from EPA's regulation of pesticide residues and should pay for the entire program. Advocates of user fees forget, however, that one of the primary purposes of federal pesticide regulation and EPA's mission are to protect the environment and to promote public health. It is a misguided representation of agency's real and laudable services to the public to characterize agrichemical companies and agricultural users as the main beneficiaries of EPA regulation.

Second, S. 722 and current law fail to provide adequate oversight of the agency's fee assessments and expenditures. It is unwise to adopt a financial system that may appear or lead to conflicts of interest. The regulated industry should not be paying EPA's salaries. Maintaining both the perception and reality of EPA's independence and integrity are of absolute importance both to the public and the agrichemical industry. In short, the user fee provision should not be a blank check for EPA and industry to negotiate. The agency must be financed and held accountable by and to the public.

Third, the fee may have a significant negative impact on the agrichemical industry and its customers. Because of economic forces, most if not all of the fees levied on pesticides will be passed on to agricultural users in higher prices. This necessity is not helpful when many farmers are already struggling. Also, such fees will further discourage registering and maintaining needed agricultural tools.

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Statement Of The Snack Food Association on S. 722 - Food Safety Amendments of 1989

The Snack Food Association (SFA) welcomes this opportunity to comment on S. 722 - the Food Safety Amendments of 1989. SFA is a non-profit international trade association representing approximately 470 manufacturers of snack foods, their associated suppliers, and equipment manufacturers. SFA members make and distribute more than 95 percent of the snacks made from vegetables, grains, fruits, meats and nuts consumed in the United States. Most of the Association's members are family-owned, moderately sized, regional businesses.

SFA members process numerous agricultural commodities that have been treated with pesticides. The vast majority of snack food products contain no pesticide residues or residues in compliance with established tolerances. Pesticides ensure the continued availability of many products manufactured by our members.

The snack food industry has great respect for the safety of the American food supply and the confidence of the consuming public. The industry has been a leader in providing meaningful nutrition information to consumers. As with other segments of the food industry, SFA is concerned about media reports that our food supply is unsafe, and that consumer confidence is diminishing. Accordingly, our association favors all efforts to review and strengthen the integrity of our nation's food supply.

SFA supports revising the food safety laws to subject all pesticide residues to the same safety standard, regardless of whether the food is in raw or processed form. S. 722, however, does not permit EPA to consider a pesticide's benefits in establishing tolerances, and imposes a negligible risk standard so strict that many pesticides would pesticides would likely be removed from the market. As written, the provisions for reviewing food tolerances could eliminate numerous safe and beneficial pesticides, and accordingly, adversely affect the safety, quality, and quantity of foods available to consumers. Accordingly, SFA opposes H.R. 1725.

The Same Standard Of Safety Should Be Applied To Both Raw Agricultural Commodities and Processed Foods

Current law provides two vastly different standards of safety for pesticide residues in food products. Raw agricultural commodities are subject to a risk-benefit standard under Section 408 of the Food, Drug, and Cosmetic Act (FFD&C Act). Pesticide residues that concentrate in processed foods above the level authorized for the raw commodity are considered food additives, and subject to the risk-only standard of Section 409 of the FFD&C Act. Section 409 contains the Delaney Clause, and prohibits any pesticide residues that are oncogenic. As a result of these two standards, carcinogenic pesticide residues may indirectly become constituents of processed foods even though they cannot be added to foods directly.

H.R. 1725 would subject all tolerances for pesticide residues to the same risk-based food safety standard, responding to the recommendation of the National Academy of Sciences to delete the Delaney Clause. SFA believes that subjecting all food tolerances to the same standard of safety will lead to greater consistency in the regulatory process and increase consumer perception that the food supply is safe.

Negligible Risk Standard Is Too Restrictive to be Meaningful

Current law recognizes the appropriateness of a negligible risk standard for pesticide residues and other hazards to which consumers are exposed. Under H.R. 1725, tolerances would be established only if the risk to human health, including identifiable populations, is negligible.

The bill, however, defines negligible risk for most chemicals as not causing or contributing to a risk of any additional adverse health effect or an adverse health effect exceeding a rate of one-in-one-million. The inclusion of "any adverse health effect" standard would be difficult for most, if not all, chemicals to meet. Pesticides are selected for their toxic effects, and it would be exceedingly difficult for a chemical to be safe for all people. Inclusion of any adverse health effect would likely approach the zero risk standard of the Delaney Clause.

Furthermore, the implementation of a statutory negligible risk definition would restrict EPA to a standard that may prove too inflexible to enforce in the future. EPA should be given some administrative discretion and flexibility to modify its standards in view of the prevailing state of the science. Should a statutory negligible risk standard prove nonworkable in the future, additional legislative oversight and amendment would once again be required.

The Benefits Of A Pesticide Must Be Considered

Current law permits the consideration of benefits in establishing a tolerance for a raw agricultural commodity but not for processed foods. H.R. 1725 eliminates all consideration of a pesticide's benefits.

Pesticides are used precisely because they have some adverse or deleterious impact on insects, plant disease, molds, bacteria, and similar pests. Food-borne illnesses may be controlled through the efficient use of many pesticides. In addition, pesticides provide benefits to the grower or user, relative to operating costs, production and yield, and revenues generated from the crops. Market benefits to consumers may be measured in terms of reasonably priced goods and quality product. Consumers expect an attractive food product that is reasonably priced. Pesticides enable food manufacturers to meet these expectations.

Snack food manufacturers enjoy many benefits from the use of pesticides. Raw materials are more abundant, available at lower prices, and less dependent on weather conditions. While consumer exposures to chemicals should be minimized to the extent feasible, a certain level of risk must be accepted when a pesticide has substantial benefits. The benefits of a pesticide, in both health and economic terms, are relevant to any policy decision.

Food Safety Regulation Must Have a National Standard

Currently, the American consumer is subject to a patchwork of various food safety regulations promulgated by state and local entities because of the perception that the federal government cannot adequately protect consumers. These often conflicting laws, however, impose substantial burdens on manufacturers in monitoring these laws and frequently confuse consumers who are presented with conflicting information on product labeling. Products frequently require different labels or ingredients to meet different local laws. Consumers ultimately bear increased product costs due to the industry's cost of compliance with various state requirements.

Pesticides Are Used Safely and Conservatively on American Products

The American food supply is safe. Data from FDA indicate that pesticide chemicals rarely are used in a manner that results in residue levels in excess of established tolerance levels. Complete overhaul of our regulatory system is not necessary at this time.

Consumers, however, perceive the food supply as containing unsafe levels of chemicals. Thus, monitoring and enforcement efforts should be strengthened to restore consumer confidence and identify problems in need of additional regulatory scrutiny. If the problem is one of resources, federal agencies should be provided with adequate appropriations to perform their functions so that state and local entities will not see a need to implement additional food safety legislation to protect their constituents.

Minor amendments to existing statutes and regulations may also be in order. Although the 1988 amendments to the Federal Insecticide, Fungicide and Rodenticide Act required re-registration of pesticides registered prior to November 1984, this law could be expanded to require periodic evaluation and re-registration of all pesticide chemicals. FIFRA could also be amended to reassess the adequacy of tolerances as part of the re-registration process. Finally, public confidence may be increased by streamlining existing procedures for cancellation and expeditious removal of hazardous chemicals.

Summary

There is no evidence that our food supply is unsafe. Recent FDA data indicate that most foods contain no residues, and that of those foods with residues, most comply with established tolerances. Americans enjoy a food supply that is safe, wholesome, and economical, and Congressional efforts should be directed toward increasing consumer confidence of these facts.

STATEMENT OF THE
AMERICAN FROZEN FOOD INSTITUTE
ON
S. 722 - FOOD SAFETY AMENDMENTS OF 1989

The American Frozen Food Institute appreciates the opportunity to comment on S. 722 - the Food Safety Amendments of 1989. AFFI is a national, not-for-profit trade association representing frozen food processors throughout the nation. AFFI members produce approximately 80% of the nation's total yearly production of frozen foods, and process numerous agricultural commodities that have been exposed to pesticides. Any change in the manner by which pesticide tolerances are established would have a significant impact on the frozen food industry.

For the most part, there are either no pesticide residues in frozen foods or the residues are well within established tolerances. This is primarily because of the judicious use of pesticides by the growers of agricultural commodities coupled with extremely effective processing methods. In many cases, however, the fruits, vegetables, and other products that AFFI members process would be rendered effectively unavailable or of substandard quality were it not for pesticides.

While AFFI supports efforts to ensure that federal laws and regulations help guarantee the safety of our food supply, AFFI opposes S. 722 because it would adversely affect the safety and availability of foods by potentially eliminating numerous safe and beneficial pesticides. In particular, AFFI believes that, while the bill appropriately would subject all pesticide residue tolerances to the same safety standard whether in raw agricultural commodities or in processed foods, the "negligible risk" standard in the bill is unrealistically rigid. Moreover, the bill's failure to consider benefits in evaluating a pesticide's safety is contrary to the public interest.

All Food Products Should Be Subject To The Same Safety Standard

Under current law, EPA establishes tolerances for pesticide residues on raw agricultural commodities. Provided that the residue in the processed food does not exceed the tolerance for the raw agricultural commodity, the finished food product is not deemed to be adulterated. If, however, residues concentrate during processing and exceed permissible tolerances in finished products, an excessive residue becomes a food additive which must be then approved by FDA. Tolerances for residues in raw agricultural commodities are not subject to the Delaney Clause. However, residues in finished foods that exceed tolerances for raw agricultural commodities may be prohibited under the Delaney Clause, if carcinogenic, regardless of the level.

S. 722 would provide for the establishment of all food tolerances under one section of the Federal Food, Drug, and Cosmetic Act. As a result, all food tolerances would be subject to the same risk-based standard of safety. The bill responds to the National Academy of Science's recommendation that pesticide residues should be evaluated by the same standard of safety, whether on raw agricultural commodities or in processed food, and whether for new or old pesticide chemicals, thus eliminating the so-called "Delaney Paradox." AFFI supports the evaluation of all food tolerances under a standard that is not dependent on the form of the product.

The "Negligible Risk" Standard Should Be Redefined

S. 722 provides that tolerances would be established only if the risk to human health, including identifiable populations, is negligible. Tolerances that would not meet this negligible risk standard would be revoked or modified.

The bill also provides a statutory definition of "negligible risk." For most chemicals, negligible risk would be the level at which the pesticide would not contribute to an adverse health effect exceeding a rate of one in a million or any additional adverse human health effects. The "negligible risk" standard is unreasonably restrictive by its incorporation of all adverse health effects. By defining negligible risk in terms of a wide range of health effects, the bill approaches the absolute standard of safety provided by the Delaney Clause.

The concept of permitting only those pesticide residues and other substances that meet a "negligible risk" standard in foods is acceptable for carcinogens and certain other chronic health effects. As currently drafted, however, the "negligible risk" standard effectively means "zero risk." This is because few chemicals, if any, would not cause some adverse reaction to some segment of the population, even if the reaction is not likely to be health threatening.

Congress should not legislate numerical risk formulations and build such formulations into statutes. Such an approach leaves no room for the exercise of administrative discretion and application of prevailing scientific knowledge which may continue to evolve. As a result, Congressional oversight on an ongoing basis would be required to monitor the appropriateness of the standard and whether any further statutory amendment might be required. Any legislation revising the current food safety laws should be flexible enough to permit administrative action when the scientific basis for the decision process changes.

Pesticides Are Important And Benefits Should Be Considered

Current law directs EPA to consider a pesticide's benefits when conducting risk assessments as part of the tolerance-setting process. This recognizes and acknowledges that, despite potential toxic effects, pesticides serve a useful function in crop production. S. 722 would prohibit the consideration of a pesticide's benefits.

To ignore the benefits of a pesticide is naive and contrary to the public interest. Many pesticides by definition have some kind of deleterious effect on insects, plant disease, mold, bacteria, and other threats to agricultural crop viability. Pesticides are primarily used to promote the growth of strong and healthy crops. While it makes sense to minimize consumer exposure to pesticide risks, a certain level of risk must be accepted where a pesticide's benefits are substantial.

Modern agricultural practices are essential to ensure a safe, wholesome and nutritious food supply. The majority of plant species are not naturally suitable for human food. Through the years, fertilizers, feed additives, and pesticides have been effectively employed to increase productivity and control pests.

Pesticides have many uses in the variety of commodities processed by frozen food manufacturers. For example, fungicides control potato blight which can reduce crop yield and quality. Pesticides are used to control nematodes in potatoes which can reduce to zero the value of a crop by reducing yield as much as 25 percent.

Fumigants control nematodes as well as soilborne diseases which can reduce production potential by 50 percent and reduce quality to the point where a crop can become entirely unacceptable for food uses. On green leafy vegetables, pesticides are used to control worms, flying insects, and the growth of fungal diseases. If the pesticide EBDC were withdrawn from the market, for example, leafy green vegetables providing substantial amounts of vitamins A and C as well as calcium could be devastated by fungal disease and rendered unavailable to consumers.

A wide spectrum of available active pesticide ingredients is essential to the continuing viability of our food supply. New and varied products must be available for crop production as pests develop resistance or immunity to a particular active ingredient. Furthermore, a wide variety of active ingredients prevents the possibility of accumulation of a single pesticide residue in the human diet.

The health benefits of pesticides, in particular, are numerous and important. Bacterial food poisoning is the largest single hazard in the food supply. Humans are susceptible to many illnesses carried by rodents, insects, and other disease vectors. Several human pathogens are spread by insects and rodents, and in the absence of effective fumigants, rodenticides, and insecticides, the incidence of these diseases may increase. Control of many diseases, including typhus and bubonic plague, have resulted from the prudent use of pesticides.

As earlier suggested, fruits and vegetables are good sources of vitamins and minerals. In the absence of pesticides, this essential nutritional source would be limited or lost. A recent report by the National Academy of Sciences entitled "Diet and Health" recommended that Americans consume five or more servings of a combination of vegetables and fruits daily, especially green and yellow vegetables and citrus fruits. Additionally, the National Academy of Sciences recommended that Americans increase their intake of starches and other complex carbohydrates by eating six or more daily servings of a combination of breads, cereals, and legumes.

The NAS Committee noted that increased consumption of vegetables and fruits could result in increased ingestions of pesticide residues which might be carcinogenic. The Committee emphasized, however, that the potentially small increased risk that could result from increased exposures in the general population would be greatly outweighed by the potential benefits to be expected by greater fruit and vegetable consumption. The NAS report concluded that the liberal consumption of fruits and vegetables poses no undue competing risk of cancer.

In short, pesticides provide many important practical benefits. The benefits of pesticides are not limited to economics, but involve the nutritional quality and availability of food. Certainly, these benefits are relevant to public policy decisions regarding permissible pesticide usage.

Minor Use Crops Would Lack Alternative Products

EPA regulations define "minor use" pesticides as those chemicals used on a crop that is planted on a small total amount of acreage or a use that has an inherently small potential market volume. The minor uses of pesticides would be particularly vulnerable under S. 722. Pesticide manufacturers would be encouraged to pursue tolerances only for those pesticide chemicals for which significant profits could be expected. Research and development funds for new pesticides would also be devoted to uses expected to yield large profits.

Most frozen foods, with the exception of crops such as corn, are considered minor use crops and therefore would not be likely to receive the attention needed from chemical manufacturers should existing products be removed from the market. Although the bill as drafted would permit any interested party to petition for a pesticide tolerance, the feasibility of anyone other than a pesticide registrant pursuing the data necessary for registration and tolerance establishment is unlikely. Additionally, unless a user group could be assured of a pesticide's continued registration, the process of obtaining a tolerance might be rendered moot by a manufacturer's unwillingness to pursue a registration.

Proper Pesticide Use Is Key To Safe Food

Contrary to media reports, recent data from FDA's monitoring program indicate that no pesticide residues were found in over 50 percent of samples analyzed. Of the total number of samples, less than 1 percent had residues that exceeded the established tolerance level. Of those samples with violative residues, 81 percent of the violations resulted because the commodity/pesticide combination did not have an established tolerance. The fact is that pesticides are safely used and residues are quite limited in frozen food. Washing an agricultural commodity prior to freezing eliminates or substantially reduces pesticide residues below the tolerance levels.

Many frozen food manufacturers impose restrictions on their fruit and vegetable growers to ensure compliance with pesticide labels. For example, a typical pesticide agreement found in a pre-season contract requires that growers use only pesticides which are appropriately registered, follow label directions, and maintain records of the amount of pesticide applied to the crop. Growers are also requested to certify that the products, when delivered to a processor, will contain no residues of any pesticide which is not safe within the meaning of the Federal Food, Drug, and Cosmetic Act. If a grower files an incomplete, untruthful, or inaccurate report, the product may be rejected or the company may refuse payment.

Additionally, many companies conduct sampling of raw materials for pesticide residues to ensure compliance. Companies frequently employ field personnel who observe pesticide use as part of their general crop monitoring practices.

Simply stated, available evidence proves that food products are safe. The key to keeping them safe is proper pesticide use.

National Uniformity In All Food Safety Legislation Is Essential

National uniformity and consistency in all food safety laws is crucial to the food industry and the consuming public. Wherever there is an inconsistency between federal, state, and local laws, federal tolerances and regulations must prevail. Should resources at the federal agencies be insufficient to monitor the food supply, adequate funding is essential.

Food processors and manufacturers are, with increasing frequency, subject to a wide range of state and local food safety laws, enacted in response to a perception that the Federal government is not adequately monitoring food safety. Often, these laws impose vastly divergent requirements that make interstate shipments and sales of identical products extremely burdensome to the food manufacturing and processing industry. For example, labels and ingredients must constantly be evaluated for compliance with various state and local requirements. The result is consumer confusion from either different labels or varying requirements for comparable products. Ultimately, the consumer will also be forced to pay for any increased costs of compliance.

If the federal regulatory agencies currently lack adequate authority to address the safety of pesticides in our food supply, additional appropriations and minor statutory changes may more readily address the problem. The 1988 amendments to the Federal Insecticide, Fungicide and Rodenticide Act already require that EPA re-register all pesticides registered before November, 1984. If additional authority is needed, FIFRA should be amended explicitly to require the reassessment of tolerances as pesticides are re-registered, and streamline existing cancellation procedures to permit the removal of hazardous pesticides from the food supply.

Chemicals will continue to play a large role in agriculture. Biotechnology and low input agriculture have the potential to reduce some environmental concerns, such as soil erosion, groundwater protection, and other health related issues associated with chemical use. At this time, however, these technologies cannot and should not provide a substitute for pesticide use. Continued availability of a wide range of pesticide products is necessary to the viability of this nation's agriculture.

Summary

Americans receive the safest and most abundant food supply in the world. Much of the credit for this goes to the responsible use of pesticides. AFFI supports the review of current laws to ensure the consumers continue to have available a variety of safe, wholesome, and economical foods. AFFI opposes S. 722, however, because it would impose impractical risk assessment standards and prohibit the consideration of important benefits in establishing pesticide tolerances.

Statement of the American Farm Bureau Federation
To the Senate Labor and Human Resources Committee
Regarding S. 722, "The Food Safety Amendments of 1989"

June 6, 1989

The American Farm Bureau Federation is the nation's largest general farm organization. Our membership totals 3.6 million member families in forty nine states and Puerto Rico. Farm Bureau members grow nearly every agricultural commodity raised commercially in the United States. We appreciate this opportunity to comment on S. 722, "The Food Safety Amendments of 1989."

For years our farmers have responded to the demands of the consumers by producing low cost, high quality food. To do this, we have turned to technology to help us design modern agricultural production systems. These systems have enabled our farmers to produce more food on less land and compete successfully on world markets. Pesticides are an integral part of these systems. Now consumers are telling us they still want high quality food but they don't want to worry about pesticide residues. Are they willing to pay higher prices for some commodities, buy a larger share of our fruit and vegetable products from overseas, accept less than perfect produce, and perhaps see some farmers go out of business? We're not sure.

But we are on the front lines. We mix the pesticides that regulators are concerned about. We live on the land where those pesticides are applied. And we rely on the consumers to buy the food we produce in order to stay in business. We can't judge the safety of the chemicals we depend on so we have to trust the scientists and the regulators to ensure that the tools we need are compatible with the environment. If a pesticide poses unreasonable risks, we need to know and we want something done about it.

As farmers, we want to do what is right for our land and what is best for our consumers. We would like to see a regulatory environment that will reinforce public confidence in the safety of our food supply and allow farmers and ranchers to use safe and economically effective production tools. Where unreasonable risks exist, pesticides must be removed in a timely and effective manner. Where objective scientific evaluations show that risks do not exist, steps must be taken to reassure the public.

It is from this perspective that we offer the following comments on S. 722, "The Food Safety Amendments of 1989". We support the concept of a negligible risk standard and the need to address the conflict in our current pesticide laws that has become known as the "Delaney Paradox".

Currently the Environmental Protection Agency establishes pesticide residue tolerances on raw foods under Section 408 of the Federal Food, Drug, and Cosmetic Act of 1954 (FFDCA). Section 408 requires tolerances at levels necessary to protect public health while insuring "an adequate, wholesome, and economical food supply". EPA does this by measuring benefits against risks and setting appropriate tolerance levels.

On the other hand, tolerances to cover pesticide residues on raw foods that concentrate in processed food products are governed by FFDCA's Section 409. This section contains the Delaney Clause which prohibits food additives found to "induce cancer" (benign or malignant tumors) in animals or humans. The Delaney Clause mandates a zero-risk limit for pesticide residues that concentrate in processed food.

Over the last decade, EPA has required that new pesticides meet the stricter standard set forth in the Delaney Clause. This has meant that many newer pesticides with low potential to cause tumors have been denied registration. Older pesticide products awaiting re-registration have yet to be brought into compliance with the Delaney Clause. The "paradox" in the law is that adherence to the zero-risk Delaney Clause prevents newer, safer but minutely oncogenic pesticides from being approved to replace older, riskier pesticides which have remained on the market. The paradox stems from the inconsistency between the zero-risk Delaney provision of FFDCA and the risk/benefit standard authorized in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Because of this inconsistency, the EPA asked the National Academy of Sciences' (NAS) Board on Agriculture to study the tolerance setting process for pesticide residues in food and its effects on food availability and the protection of public health. The NAS panel was asked to analyze the oncogenic or tumor-causing risks of pesticides by pesticide type, crop, and type of tolerance. Since data on actual residues is scarce, the NAS had to assume a "worst-case" scenario. These "worst possible assumptions" reflect the maximum amount of risk that is sanctioned by law, given current tolerances. They do not reflect the amount of risk actually present in the diet. The key assumptions used by NAS were that 100 percent of each crop was treated with every pesticide registered for use on that crop and that residues remaining on the crop were at the full tolerance level. In other words, NAS looked at hypothetical cases where residues would be present in foods at the full tolerance levels. This "worst case" analysis found that nearly 80 percent of the estimated dietary oncogenic risk was from residues of 10 pesticides on only 15 different foods. NAS also found that EPA regulatory actions taken to comply with the Delaney Clause ironically failed to reduce unreasonable risks and sometimes even increased them.

The NAS panel studied the implications of four policy scenarios for regulating residues in foods. They found that adoption of a negligible risk standard (defined as an additional one in a million risk of contracting cancer following a lifetime of exposure) would achieve the desired effect of removing older riskier pesticides while allowing newer safer pesticides to be registered. Under a negligible risk standard applicable to residues on both raw and processed food, most of the total risk was eliminated while only a few of the benefits (as measured by acre treatments and costs) were lost. On the other hand, strict application of the Delaney Clause, as written, would result in less risk reduction and more loss of benefits.

S. 722 attempts to address some of the issues reviewed by the NAS report. Its stated goal is "to enhance our ability to safeguard the public health while giving due weight to the interest of farmers, the food industry and chemical companies". We will work with you in attaining this goal. In our opinion, however, the bill is inconsistent with the NAS report in several important areas. We are concerned that S. 722 as written will be unnecessarily harsh on farmers and ranchers. We have the following specific comments:

NEGLIGIBLE RISK

1. Negligible risk is defined much more strictly in this bill than in the NAS study. S. 722 defines negligible risk in terms of the health of those who may theoretically be at higher risk (for example, infants and people who eat a lot of any given food), rather than in terms of the health of the average consumer. This, in effect, requires EPA to determine two things. First, do certain identifiable population groups have special consumption patterns that put them at higher risk from pesticide residues? Second, are these groups uniquely more susceptible to the residues in question (for example, rapidly developing children or older people with failing digestive systems)? The scientific expertise and data to act on this definition of negligible risk is currently scarce. Does your committee really want EPA to wait until we have enough information to make these judgments scientifically?

If the intent of the committee is to remove as much dietary risk as possible as quickly as possible, we recommend that the negligible risk standard be calculated using routine dietary exposure measures (average U.S. consumption patterns). This standard can be used during the first two year phase of risk reduction. Later, when EPA obtains a comprehensive data base and better methods to protect special risks faced by infants and other sensitive population groups, the standard could be adjusted if necessary. It is important to point out that the NAS report determined that most of the estimated dietary risk attributed to pesticides we currently use will be removed by the first risk reduction phase.

A less practical option is to restrict the use of problem pesticides on foods grown specifically for subpopulations. This is already being done to some extent on crops being grown for baby food through contracts between growers and food processors.

PHASED RISK REDUCTION

2. According to the bill, within two years of enactment, each food exposure of any given pesticide on a crop must be less than the negligible risk standard. Within four years of enactment, all of the food exposures of a pesticide, in total, must be less than the negligible risk standard. Within six years, all of the dietary exposure to pesticides from any food must be less than the negligible risk standard. We like the concept of a step-wise approach to risk reduction although we have some major reservations with this approach.

A. First, with the two year time limit on the initial risk reduction phase, our farmers have only one year in which to use the product in question and obtain the necessary residue data. Otherwise, EPA will assume that residues occur on all authorized raw foods and processed foods at the tolerance levels and that exposure occurs for a lifetime. This situation rarely occurs. For example, the Florida Department of Agriculture, in residue samples taken between 1984-1987, found that benomyl residues on oranges averaged 0.87 ppm (tolerance = 10 ppm), folpet residues on lettuce averaged 2.2 ppm (tolerance = 50 ppm), permethrin residues on lettuce averaged 1.7 ppm (tolerance = 20 ppm), benomyl residues on tomatoes averaged 0.06 ppm (tolerance = 5 ppm), and chlorothalonil residues on tomatoes averaged 0.01 ppm (tolerance = 2 ppm).

In one cropping season it will be nearly impossible to conduct the many complicated tests necessary to determine expected actual residue levels for pesticides which will be affected by the bill because of tolerance reductions. Farmers will need this information on actual residue levels to determine application rates, frequency of application and efficacy. By the second growing year, if the farmer uses a pesticide with a substantially lowered tolerance, he risks not being able to market his crop if actual residues on it exceed the negligible residue standard.

We are concerned that we won't be able to figure out what the actual residues are out in the field in one year's time. Good science usually requires replicates before researchers are comfortable with the data. Resorting to the use of tolerances to calculate risk in lieu of actual residue data may pose problems, especially in areas which are reliant on many chemicals to produce high quality, blemish-free produce.

EPA and our farmers will have to work together to determine actual use patterns and anticipated actual residue levels. Our farmers are willing to help. For example, in fall of 1988, the California Fresh Market Tomato Advisory Board implemented a "Chemical Use Screening Program" to establish a data base of chemical use patterns on fresh market tomatoes in California. The data base will eventually be used to determine actual residue levels. This information will then be available for submission to EPA or the California Department of Food and Agriculture for incorporation in both determination of pesticide use patterns and the tolerance assessment and risk assessment system. The

California celery industry is following suit. Although the data collection is voluntary, a 85 to 95 percent response rate from tomatoes and celery growers is expected.

Developing an actual residue database for all pesticides utilized in all states will be a very costly and long term undertaking. Even with joint cooperation between the private and public sector, it will take years. Logic dictates that we should concentrate on those pesticide-crop combinations that may present greater risks. Some states already have systems in place for prioritizing their residue monitoring program activities (e.g. the Florida Department of Agriculture).

B. Secondly, after the first phase of risk reduction is completed under S. 722 (negligible risk for each crop use for each pesticide), the subsequent phase would occur during the next 2 years. It seeks to reduce to a negligible risk level, the risk from all food uses of each pesticide when added together. This approach would be inconsistent with one of the NAS report's key suggestions. NAS specifically urged EPA not to base regulatory actions on risk assessments one pesticide at a time, across all of its crop uses.

Instead, the NAS report suggested that EPA base its regulatory decisions on the evaluation of comparative risks and benefits from the use of all pesticides registered for control of a given category of pests on a given crop. Otherwise, EPA regulatory actions could sometimes increase unreasonable risks after farmers make adjustments in the pesticides they use. This paradox is well documented in the NAS report.

The NAS study looked at a crop-wide risk management approach after considering the unique problem our growers will face with fungicides if a negligible risk standard goes into effect. Approximately 90 percent (by weight) of all fungicides now in use are considered potential oncogens. They are especially important in the production of many high-value fruit and vegetable crops in the eastern and southern regions of our country. The eleven fungicides studied by NAS represented less than 10 percent of the pesticides used in the field but accounted for 60 percent of the estimated dietary risk. Compounding the seriousness of this finding is the fact that the easy chemistry has been used up -- new, safe, and effective fungicides will be hard to come by. For this reason, NAS examined a cropwide tolerance reduction as a means for reducing estimated dietary risks. The NAS panel estimated that this approach could reduce the total estimated dietary risk from fungicides by up to 50 percent with only minor adjustments by farmers.

We recommend that S. 722 be amended so that a cropwide approach is used to reduce risks in this second phase. EPA can then weigh the benefits of each pesticide against the others in making the risk reduction goal. For example, EPA may see fit to allow a pesticide to remain on the market despite a higher risk but put rotational restrictions on the label. Such a pesticide might only be used every second or third year. Such a strategy is especially important when dealing with certain pesticides, particularly fungicides, which face resistance problems. Alternately, EPA could adjust pre-harvest intervals to meet the negligible risk level. A third possibility would be to allow prescription use of certain pesticides within approved Integrated Pest Management programs. It is critical that EPA retain the flexibility to take novel approaches in attaining the negligible risk standard.

It is also important to recognize that the second phase reduction period (which seeks to bring all of the food exposures of any one pesticide into line with the standard) penalizes those pesticides which have many uses. It may exacerbate the risk trade-off phenomena where farmers are forced to choose other products which may have even greater environmental risks (such as leaching into groundwater).

SETTING STANDARDS

3. The negligible risk standard should be carefully assessed by independent and government regulatory scientists and legal experts to assure that it can be administered without great delay awaiting new science and data and without vulnerability to legal challenge. Our farmers want this issue dealt with quickly, objectively, and scientifically.

EXPOSURE ASSESSMENT

4. Regarding exposure to pesticide residues, we need to keep in mind that not all of our crop acreage is treated and that pesticides may be used in some regions but not in others. Farmers generally choose pesticides on the basis of their pest problems, on whether or not that pesticide works well in their area of the country, and on the cost-effectiveness of that pesticide compared to others that are available. In other words, any given pesticide, although registered for national use, may actually be used only in certain regions or may be more prevalent in some regions than in others. In addition, many fruits and vegetables are shipped all over the country. Where the food goes is critical to an understanding of who is exposed to pesticide residues and how large that exposure is.

We also question the purpose and feasibility of attempting to calculate the amount of residue that could occur if the chemical is used illegally. Overall, this section of the bill seems to mandate many of the assumptions and practices currently used by EPA.

COORDINATION WITH FIFRA

5. The 1988 reauthorization of FIFRA has set a nine year time limit for pesticide re-registration. This is an extremely important process and it will bring about major risk reductions. EPA, the chemical manufacturers and the

agricultural community are already gearing up to comply with these tight deadlines. S. 722 would reduce these deadlines even more. The conflicting time frames of S. 722 as now written versus the FIFRA re-registration time limit for pesticide re-registration could impose severe strains on the regulatory agency, the chemical manufacturers and the entire agricultural community. We do not want to see the re-registration process compromised.

CONSISTENCY IN DATA COLLECTION

6. It is critically important to establish some consistency in the standards that will be used to collect pesticide residue data. Such a massive undertaking will likely involve both the public and private sector. We need to keep the methodology consistent so that the results will be meaningful. In addition, there is a real need to establish a correlation between the practices that are used to apply the pesticide and the residues that result from that application. In other words we will need to know how the pesticide is applied, how much is applied, where it is applied and under what climatic conditions it is applied.

INERT INGREDIENTS

7. The requirements for collecting data on inert ingredients are controversial. The expansion of the definition of "pesticide" to include inerts and degradation products is unprecedented and should be examined very carefully. As users of pesticides and consumers of food, we agree that testing for some inerts should be conducted. We are not qualified to judge which inerts should or should not be tested. We are concerned about striking the right balance between no regulation and over regulation. We need to protect users and consumers from those inert ingredients that may pose an unreasonable risk. However, we should have a system of review that provides EPA with flexibility and discretion to make judgments about which inerts to test. From an agricultural perspective, an overly rigid and mechanical approach to inert ingredients could adversely affect the cost and availability of necessary pesticide products without adding any more meaningful protection.

BENEFITS CONSIDERATION

The questions of benefits consideration is a complex, and admittedly, imprecise science -- as is the calculation of risk. As farmers, we believe that the benefits of pesticide use should be considered. The difficult decisions in calculating the value of benefits are not a problem in the extreme cases but they are a problem in the mid-range. Clearly, no one is concerned about risk/benefit balancing when there is no risk. Conversely, there are obvious cases where the risks are so apparent that benefits pale in comparison. In establishing a policy of negligible risk, the question we must consider is how hard and firm is the standard? Are there circumstances where benefits to consumers, public health, the environment, farmers and rural economies may warrant some flexibility in the standard? The negligible risk standard is a somewhat arbitrary number. The regulatory agencies approach tolerances and risk assessment in a very conservative manner. Understandably, we would rather err on the side of safety than to court the remote possibility of a risk we had inadvertently failed to consider. Thus, we assume maximum exposure to a maximum dose and factor in at least a 100-fold margin of safety. The many conservative additive assumptions we make to achieve that extra margin of safety should not be overlooked when the benefits are significant.

We believe that American consumers have benefited from a public policy that permits some marginal risks to be taken in certain circumstances when the benefits or costs are potentially significant. The business of farming and producing food and fiber is plagued with uncontrollable variables. The safe use of agricultural chemicals has, in part, helped reduce those risks and, in turn, has benefited consumers here and abroad. Fifty years ago, the American farmer produced enough food to feed himself and eight other people. You could not buy fruits and vegetables out of season. Nutritional deficiencies were common and the life expectancy of the average adult was considerably lower. Today, with farmers numbering about 2 percent of the population, we feed more than 100 people in addition to ourselves and export 30 percent of our production. Life expectancy has increased and nutritional deficiencies have largely disappeared. As we view it, society has benefited tremendously from our production capabilities. We would strongly urge the committee to give serious thought to the continued consideration of benefits.

UNIFORM RESIDUE TOLERANCES

Any legislation to revise and strengthen the federal tolerance setting process for pesticide residues on food should also include a provision establishing uniformity across the country for individual tolerances. There are no logical health or safety reasons for allowing different states to establish conflicting residue levels for the same pesticide. On the other hand, there are a number of concerns about the chaos that would result in marketing and farm management if such practices were followed. State by state tolerance setting would unduly burden interstate and foreign commerce.

AVAILABILITY OF ALTERNATIVES

If we are committed to maintaining a safe and bountiful food supply, we must have economically viable alternatives for those pesticides that are removed from the market. We agree that the safety of our food supply and our environment is of critical importance. But we also think the nutritional quality of our food and the viability of our agricultural sector is equally important.

In a study of corn and soybean pesticides and the potential effects of regulatory decisions concerning them, the Economic Research Service (ERS) concluded that banning one pesticide would have little effect on a pest problem but that banning all pesticides could have substantial effect (Osteen and Kuchler, 1986, Ag. Economic Research Report no. 546). They also found that some pesticide users would suffer significant losses even though the aggregate effects of banning a particular chemical were small. The ERS concluded that the availability of alternatives was critical. Likewise, the availability of alternatives is an important component of the EPA risk/benefit analystis required by FIFRA. We need to ask ourselves whether or not we have workable alternatives for discontinued pesticides.

An even more important question is whether farmers can use these alternatives in the management systems they currently have access to or can successfully utilize. We believe strongly that the agricultural community should be given both the opportunity and the incentives to use Integrated Pest Management (IPM) programs. IPM has a sound scientific basis and a fifteen year track record in terms of saving money, protecting the environment and maintaining the quality of the end product. Currently IPM suffers from a lack of funding and a lack of well defined goals. We have described eleven major areas in which steps could be taken to improve IPM research programs, accelerate technology transfer to farmers, and make IPM a national priority. We would like to enter our findings into the record along with our testimony today and we urge the Committee members to take a look at them.

One of the major concerns of many researchers is that when we lose pesticides without assessing their value in IPM programs, we may make it even more difficult to establish successful IPM programs. IPM utilizes a variety of techniques which are finely meshed together to keep pest populations below damaging levels. Permanent pest suppression can sometimes result through the successful establishment of predators and parasites, environmental modifications, changes in cultural practices, or the use of resistant crop varieties. Pesticides are used only when necessary and appropriate but they are critical in a systems approach. A good example is cyhexatin (Plictran). Cyhexatin was a miticide that was especially useful to IPM apple and citrus growers because it did not harm predatory mites. When EPA received a study indicating that cyhexatin could cause birth defects in rabbits, they quickly acted to remove it from the market. IPM programs were suddenly left without a valuable tool (in this case, dietary risk was not considered to be important).

We also need to help farmers who are willing to make changes. First of all, we need to remove some of the disincentives in our system. We have identified several disincentives to widespread IPM adoption in our analysis of IPM use among farmers. We also need to realize that the transition from a chemically intensive farming system to a chemically minimal farming system is difficult. The Rodale Institute found that it took roughly five years for the natural balance of nature to re-establish itself.

ENCOURAGING INNOVATIONS IN AGRICULTURE

To help our farmers in the future, it is absolutely critical that we create a positive climate for innovation within the agricultural sector. The costs and time it takes to register new pesticides are absolutely staggering. The NAS report documented the problems and costs currently encountered by industry in attempting to respond to demands for safer chemicals. They also surveyed the Pesticide Research and Development Directors of the major pesticide manufacturers to determine how current laws affect agricultural pesticide research productivity. We urge you to pay close attention to this section of their report. Science can deliver markedly improved pest control technologies, but whether it does so will depend largely on public policy.

In conclusion, we support the use of a negligible risk standard for pesticide residues, providing consistency in the federal law. We believe that such an approach should follow the full intent of the NAS report which balanced reasonable risk reduction with the necessity of retaining useful production tools for farmers to use. We are concerned that S. 722 as written may not be in the best interests of consumers and farmers. However, if all of the NAS recommendations were followed, we think we could achieve a meaningful reduction in unreasonable pesticide residue risks to our consumers with minimal impact on our food supply and the viability of our agricultural sector.

Thank you for giving us the opportunity to express the views of our members. We look forward to working with you in a positive and constructive way.

Attachment to Testimony
American Farm Bureau Federation
June 6, 1989

INTEGRATED PEST MANAGEMENT: A NATIONAL PRIORITY

Integrated Pest Management (IPM) is a systems approach to safely reduce pest damage on crops while maintaining quality and yield goals. First the amount of injury which can be sustained by the crop without damaging yields is determined. This is correlated with pest density. Pest populations are then monitored in the field. Treatments are recommended only when pest populations rise above the predetermined thresholds.

A variety of techniques are utilized to keep pest populations below damaging levels. Permanent pest suppression can sometimes result through the successful establishment of predators and parasites, environmental modifications, changes in cultural practices, or the development of resistant crop varieties. In all cases, pesticides are used only when necessary and appropriate.

Currently, IPM programs are evolving towards a total systems management approach to farming. All of the variables that influence the development of the crop are considered: soil, water, light, microclimate, crop growth, pests, diseases, etc. In some programs, farm economics are also taken into consideration.

IPM programs have been under development for the last 15-20 years. They have a proven track record in terms of saving the farmer money either by decreasing input costs or by improving the quality of the end product. IPM programs have reduced pesticide use considerably on some crops. Typically, fewer applications per season on fewer acres are now needed. But the potential reductions could be considerably more. The Office of Technology Assessment estimates that we could reduce insecticide use in U.S. agriculture by as much as 75 percent if IPM programs were widely adopted.

IPM programs are normally crop-specific and site-specific since pest complexes on crops vary from region to region. Estimates on the percentage of crops grown under IPM practices (when defined as the use of two or more tactics for pest suppression) show that large percentages of the apples, alfalfa, cotton and soybeans grown in the U.S. are under some form of IPM. But in general, the percentage of total cropland under IPM is probably closer to 25 percent.

HISTORY OF IPM

At the present time, the USDA is the lead agency in developing IPM programs. Back in the late 1960's and early 1970's, the USDA and National Science Foundation, later joined by the newly formed Environmental Protection Agency, launched several national IPM research programs. In 1972, the Huffaker Project, directed by Dr. Carl B. Huffaker at the University of California at Berkeley, began with universities in 18 states and over 300 scientists participating. The six year project focused on insect control in alfalfa, cotton, soybean, citrus, pome and stone fruits, and pine forests (primarily bark beetles).

During the same period, funds were provided to the Cooperative Extension Service (CES) by the USDA to begin development of pilot pest management programs. From 1971 to 1975, 39 federally funded pilot pest management projects were started in 29 states by CES. The Cooperative Extension Service IPM programs were based on the use of field scouting to determine whether or not insecticides should be applied. Later CES programs included management of weeds, diseases, and nematodes, as well as insects. Today, virtually every state conducts an extension IPM program.

Following the Huffaker Project in 1979, a similar program was initiated by Dr. Perry L. Adkisson at Texas A & M University. The Consortium for Integrated Pest Management (CIPM) was made up of 17 states and involved over 250 scientists. It continued and expanded the use of systems study and modeling to better evaluate complex crop/pest interactions. CIPM focused on studying the effects and minimizing damage of insects, weeds, diseases, and nematodes to four major crops: apples, alfalfa, soybeans, and cotton. It ended in 1985.

Recognizing a need for a national IPM approach, the USDA began considering how best to develop a coordinated framework in 1980. In 1982, the National IPM Coordinating Committee was established. The committee was made up of administrative and technical representatives from an alphabet soup of acronyms: the Agricultural Research Service (ARS), the Cooperative State Research Service (CSRS), the Extension Service (ES), the Economic Research Service (ERS), Consortium for Integrated Pest Management (CIPM), Regional IPM administrative advisors and chairpersons, and administrative representatives from the Experiment Station Committee on Policy (ESCOP), the Extension Committee on Policy (ECOP), and the Resident Instruction Committee on Policy (RICOP). Its current membership consists of representative Experiment Station Administrators, staff members from CSRS, and Department Heads from each of the regions. This committee oversees the national IPM program: four regional IPM projects working on 12 commodities, each directed by four regional committees. The four regions and the priority commodities included in the National IPM Program are:

West: range, alfalfa, small grains, tree fruits, potatoes
North Central: potatoes, corn, confined livestock
South: soybeans, cotton pecans, peaches, alfalfa
North East: potatoes, forage crops, tree fruits

In FY-1985 a total of 77 projects encompassing the 12 commodities were funded, adding up to about $2.8 million. Like most IPM research projects, the national effort suffers from inadequate funding and the uncertainty that accompanies "soft" money. Grants are renewed on a annual basis so that researchers do not know from year to year whether their project will be refunded.

ACHIEVING THE WIDESPREAD USE OF IPM

The widespread use of IPM among farmers will only be accomplished if we re-establish IPM as a national priority. Currently, IPM suffers from lack of funding and lack of well defined goals with research and technology transfer being parceled out among CSRS, ES, ARS, APHIS, and even EPA. The

National Coordinating Committee is a step in the right direction but it is only a committee and lacks the statutory authority to ensure adequate coordination between agencies and discourage "turf battles" among participants.

To develop, coordinate, and carry out a national strategy for IPM research and technology transfer, we propose the establishment of a new office within the USDA. This Office would report to the Assistant Secretary for Science and Education.

The Office of Integrated Pest Management (OIPM) would be given the responsibility to provide administrative support for developing and coordinating departmental policies and activities pertaining to IPM research. It would also carry out related interagency and public liaison staff functions. The OIPM would be specifically responsible for the following:

1. The OIPM would oversee the functions and activities of the IPM National Coordinating Committee.
2. The OIPM would assist in the development and implementation of policies as recommended by the IPM National Coordinating Committee.
3. The OIPM would maintain records of the IPM research and technology transfer activities carried out under the authority of the Secretary of Agriculture.
4. The OIPM would be responsible for coordinating activities with other federal agencies. Specifically, OIPM would work with EPA on registration of biopesticides and replacement control methods for canceled pesticides. OIPM would also work with NSF to help direct research at the National Centers for Excellence in IPM (see below).

In addition to the OIPM, we need to reaffirm our total national commitment to IPM. We can accomplish this by offering incentives to farmers to aid them in making the transition to IPM programs and by removing disincentives that discourage use of IPM techniques such as crop rotations and biopesticides.

The following recommendations are designed to improve IPM research programs, accelerate technology transfer to farmers and make IPM a national priority.

1). ACCELERATED REGISTRATION OF BIOPESTICIDES: We need a wider variety of highly selective, environmentally-sound, IPM compatible pesticides to increase the effectiveness of IPM programs. The registration of biopesticides such as pest disease agents, insect pheromones, and other alternative methods of pest control can be encouraged in a number of ways. These include the streamlining of registration procedures and the re-evaluation of registration requirements.

2). USE OF IPM BY FEDERAL AGENCIES: All federal agencies, including the military, should adopt the most suitable IPM technology available on all lands leased or owned by the federal government. Agencies should use all fiscal, programmatic, and regulatory mechanisms to encourage the development of IPM in all sectors. Although required to do so back in 1972, there is some question as to how widespread compliance has been.

3). SUPPORT OF RESEARCH AND DEVELOPMENT: IPM programs are dependent upon the availability of qualified personnel, the adequacy of the data base, and the successful integration of that data into a workable system. The continued support of IPM research is vital. Examples of programs that should be encouraged include:

a). a national resistance monitoring system to identify pest resistance problems before they become widespread.

b). a national pesticide monitoring system to identify problem pesticides (pesticides likely to be withdrawn from the market due to environmental problems). Our greatest problem with canceled pesticides is the economic hardships caused by the lack of suitable replacements -- either alternative pesticides or economically viable alternative control tactics. If we can do a better job of pinpointing problem pesticides, we can get a headstart on developing alternatives. Industry-government projects should be encouraged in this area.

In addition to funding the above programs, funding agencies need to recognize the need for interdisciplinary research in IPM. Although funding of individual projects should continue, more funds should be directed towards group projects to encourage cooperation across departments and disciplines (for example, a joint project on strawberry IPM involving entomologists, plant pathologists, agronomists, weed scientists, etc.).

4). IPM TRAINING: IPM training should be incorporated into all pesticide applicator training programs. All commercial and private pesticide applicators should be aware of IPM tactics and the value of using chemicals judiciously. Incorporating this type of training into these programs would reach a majority of farmers.

There is also a need to educate loan officers about new management techniques. They are responsible for lending farmers money and, if unfamiliar with IPM, may require the farmer to continue to use conventional production management techniques.

5). EXTENSION IPM PROGRAMS: The Extension Service has recommended improvements in the following areas and we concur: 1) educating agricultural chemical dealers and sales personnel; 2) providing interdisciplinary training for extension IPM specialists; 3) involving consulting firms more directly to encourage rapid technology transfer; 4) developing interdisciplinary research teams to address problems; 5) providing more direct access to research results; and 6) placing more emphasis on the training of IPM scouts.

6). EXAMINATION OF THE EFFECTS OF CONTRACTUAL AGREEMENTS ON IPM USE: The excessive use of pesticides may be encouraged by the lending procedures used by banks making agriculturally related loans. For example, banks may require routine calendar spraying to protect their investment. In addition, the cosmetic standards set by the food marketing and processing industry may exceed those necessary for storage and to preserve taste and nutrition. Both possibilities should be examined and, if necessary, changes made.

7). USE OF PESTICIDES EXCEEDING NEGLIGIBLE RISK STANDARDS WITHIN APPROVED IPM PROGRAMS: EPA should undertake an environmental risk- benefit study of the possibility of restricting higher risk pesticides to use within approved IPM programs. In other words, if a pesticide's safety or environmental effects are in doubt, then its use would be allowed only in IPM programs that minimize risk and maximize benefits.

8). IPM IMPACT STATEMENTS FOR PESTICIDE REGISTRATION: As part of the development process, companies should be encouraged to test novel pesticides within operating IPM programs early on in their testing programs. The registration process would favor those pesticides that have been proven compatible with existing IPM programs on the appropriate crops.

9). ESTABLISHMENT OF CENTERS OF EXCELLENCE FOR IPM: The National Research Council is recommending that the National Science Foundation establish regional Centers of Excellence for IPM. Researchers from many disciplines would be encouraged to interact and blend existing and developing technologies into workable IPM programs.

These centers will be especially important if we are to achieve the immediate and successful incorporation of products generated through agricultural biotechnology into IPM programs.

10). EXAMINATION OF THE EFFECTS OF FARM PROGRAMS ON IPM USE: We need to examine our farm programs to determine whether or not they encourage or discourage the use of IPM tactics. Program versus non-program crops can influence rotation practices. For example, the base acreage provisions in corn can influence crop rotation practices. Crop rotation is a very effective way to minimize recurring pest problems.

11). SEPARATE LABELING FOR IPM-GROWN PRODUCE: There appears to be a market for produce that has been grown under environmentally safe techniques. Certainly, there has been consumer interest in organically grown produce (although its comparative expense and blemished appearance discourages many prospective customers).

To identify producers who use IPM, the USDA could establish an IPM Registry to certify IPM growers through the Cooperative Extension Service. Most likely such a system would have to operate at the county level to permit adequate monitoring to guarantee compliance. Growers who meet Registry Standards would be granted the right to use the PUREST label: "Produced Under Registered Environmentally Sound Techniques."

PREPARED STATEMENT OF THE NATURAL RESOURCES DEFENSE COUNCIL

Thank you for the opportunity to testify before this Committee about S.722, the Food Safety Amendments of 1989. I am Janet Hathaway, senior project attorney with NRDC. The Natural Resources Defense Council (NRDC) is a non-profit organization of attorneys and scientists dedicated to protecting public health and the environment.

NRDC has recently released a study, "Intolerable Risk: Pesticides in our Children's Food"[1], which documents that the risks from actual residue levels of 23 pesticides used in 27 fruits and vegetables greatly exceed even the government's own standards for acceptable risk. In the decade NRDC has been working to improve pesticide policy, NRDC has released a book entitled Pesticide Alert[2], frequently presented testimony before this and other Congressional committees, and issued numerous reports documenting serious flaws in our regulations and laws concerning pesticides.[3] NRDC was also centrally involved in the effort to reform the regulation of pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Some key elements of the reform proposals advanced by NRDC were included in legislation the Congress enacted last year.[4] We have also sought improvements to the Federal Food, Drug and Cosmetic Act (FFDCA), the law that governs pesticide residues in food.

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[1] B. Sewell, R. Whyatt, J. Hathaway and L. Mott; "Intolerable Risk: Pesticides in our Children's Food," Natural Resources Defense Council, February 1989.

[2] Lawrie Mott and Karen Snyder, Natural Resources Defense Council, Pesticide Alert: A Guide to Pesticides in Fruits and Vegetables, 1988.

[3] Hearne, S., "Harvest of Unknowns: Pesticide Contamination in Imported Foods," NRDC, 1984; Mott, L. and Broad, M., "Pesticides in Food: What the Public Needs to Know," NRDC, March 15, 1984; Mott, L., "Pesticide Reregistration: An Evaluation of EPA's Progress," NRDC, April 3, 1986.

I. CURRENT LAW DOES NOT PROVIDE ADEQUATE PUBLIC HEALTH PROTECTION FROM PESTICIDES IN FOOD.

NRDC has identified many serious deficiencies in our federal program to protect the public from pesticides in food. Among the most fundamental are the following:

> ***EPA has incomplete or inadequate toxicological and residue chemistry data for many of the nearly 300 pesticide active ingredients used in or on food. The legal limits for residues of pesticides remaining in food (or "tolerances") were established for many pesticides before the Agency had information on the long-term effects of dietary exposure. When EPA receives new data on a pesticide's potential to cause cancer, birth defects, reproductive disorders, or other deleterious consequences, EPA does not rapidly reassess and revise tolerances to reflect the best available safety data.
>
> ***Ingredients which do not kill, repel or control pests, misleadingly termed "inert" ingredients, are not adequately regulated, although many may cause equally serious adverse effects as "active" ingredients.

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[4] Federal Insecticide, Fungicide and Rodenticide Act Amendments of 1988, Pub. L. 100-532, October 25, 1988.

***EPA lacks authority to act immediately to modify or revoke tolerances even when new information indicates an extreme risk to public health.

***EPA grants tolerances for pesticides even in the absence of a practical analytic method for measuring the residues in foods. The agencies which enforce tolerances, the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), are forced by their limited equipment and resources to rely almost exclusively on multi-residue analytical methods. The agencies are unable to detect nearly half of the pesticides for which EPA has set tolerances using multi-residue methods.

***EPA has interpreted the FFDCA to condone the presence of carcinogenic pesticides in raw food and in certain processed foods. EPA has argued that a risk-benefit analysis is appropriate for determining when carcinogenic pesticides can be used on raw foods.

***Although the FFDCA contains a provision--the "Delaney clause"--which prohibits the use of certain carcinogenic pesticides in food, EPA has invoked the Delaney clause infrequently and never with respect to pesticides which have been on the market for many years. Old pesticides pose some of the greatest dietary hazards, but EPA allows the continued, widespread use of old, carcinogenic pesticides in food.

S.722 is an important public health protection bill. It would correct the most serious defects in our current programs to control pesticide residues in food. The solutions offered by the bill fall short of the ideal. Most notably, S.722 does not eliminate all cancer-causing or otherwise dangerous pesticides from our food supply. However, the bill does require that such pesticides must be used in a way which will ensure that residue levels pose relatively low risks. S.722 would markedly improve food safety and is urgently needed to restore the public's confidence in our food supply.

II. EPA HAS NOT ENFORCED THE DELANEY CLAUSE TO PROTECT THE PUBLIC FROM CARCINOGENIC PESTICIDE RESIDUES IN FOOD.

S.722 would eliminate the application of the Delaney clause to pesticides and require the EPA to instead apply a "negligible risk" standard to pesticides used in food. NRDC concludes that the application of the negligible risk standard of S.722 to all foods--whether raw or processed--would in fact improve food safety. This is so because the Delaney clause has limited application to pesticides in food, and because EPA has not enforced the Delaney clause even when by the terms of the FFDCA the clause should prohibit the use of a pesticide on certain foods.

People may assume that carcinogens in food are illegal, thanks to the Federal Food, Drug and Cosmetic Act's famous "Delaney clause". Unfortunately, this is not true. The Delaney clause does not even prohibit all carcinogenic pesticides in food. The Delaney clause only rules out the use of some cancer-causing pesticides (i.e., ones that concentrate during processing and ones used in post-harvest treatments) on some foods (processed foods). Moreover, even when Delaney clause does apply, the agencies charged with its implementation have routinely ignored or cleverly side-stepped the restriction.[5]

Only twice in the three decades since Delaney became law has EPA invoked the clause to refuse a new food use of a carcinogenic pesticide.[6] Neither EPA nor FDA has ever cited the Delaney clause to justify banning an existing food use of a carcinogen since Congress overturned FDA's attempt to ban saccharin in 1977.[7]

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[5] Congress itself created some exclusions from the application of the Delaney clause, including the 1962 DES proviso and the clause exempting substances permitted as food additives before 1958 (the "prior sanction" exception). Numerous legally questionable exceptions to the Delaney clause have also been devised by the FDA, including the "sensitivity of method" (SOM) policy, "secondary mechanism" exception, the "constituents policy", and FDA's recently overruled "de minimis" interpretation. See National Academy of Sciences, Board on Agriculture, Regulating Pesticides in Food: The Delaney Paradox, 1987, hereinafter NAS, pp. 37-40; Richard A. Merrill, "FDA's Implementation of the Delaney Clause: Repudiation of Congressional Choice or Reasoned Adaptation to Scientific Progress?", 5 YALE J. ON REG. 21-29, 41-49 (1988); and Public Citizen v. Young, 831 F.2d 1108 (D.C. Cir. 1987).

[6] EPA cited the Delaney clause for its denial of tolerances for the pesticides fosetyl al and permethrin. NAS, supra, pp. 92-93. FDA invoked the Delaney clause only four times to prohibit the use of a substance in food. Merrill, supra, p. 9.

[7] Saccharin Study and Labeling Act, Pub. L. No. 95-203, 91 Stat. 1451 (1977).

The Federal Food, Drug and Cosmetic Act (FFDCA) includes two provisions which provide the authority for EPA to establish legal limits for pesticide residues in food ("tolerances") and for FDA to monitor and to enforce pesticide tolerances. Section 409, including the Delaney clause[8], applies to food additives. Pesticides are considered food additives only when they occur in processed foods where cooking or other processing methods cause residues to concentrate above the legal limits for raw food.[9] Such concentration occurs in certain heat-processed foods such as applesauce, raisins and tomato paste. For processed foods with concentrated pesticide residues, the Delaney clause prohibits any pesticide "if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . ."[10] Most commentators, including until recently both FDA and EPA, interpret the Delaney clause as a categorical prohibition on the use of cancer-causing substances within its scope. FDA's effort to re-interpret the Delaney clause to permit the use of color additives posing cancer risks less than one in a million through an implicit de minimis exception was rejected by the D.C. Circuit.[11]

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[8] In the Federal Food, Drug and Cosmetic Act, there are actually three Delaney clauses, one for each of three categories of substances--food additives, color additives, and animal drugs--which may leave residues in food. Pesticide residues are regulated by the food additives Delaney clause, which was added to the statute in 1958.

[9] FFDCA's definition of "food additive" excludes "pesticides on raw agricultural commodities." 21 U.S.C. § 321(s). Also exempted are processed foods "where the concentration of residue . . . is not greater than the tolerance prescribed for the raw agricultural commodity." *Id.* at § 402, 21 U.S.C. § 342(a)(2)(c).

[10] Federal Food, Drug and Cosmetic Act, § 409(c)(3), 21 U.S.C. § 348(c)(3).

Many methods of food processing apparently reduce pesticide residues. For such processed foods and for raw foods, the products are legal if they comply with the provision of section 408. Section 408 reads:

> "The Administrator shall promulgate regulations establishing tolerances with respect to the use in or on raw agricultural commodities of poisonous or deleterious pesticide chemicals and of pesticide chemicals which are not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of pesticide chemicals, as safe for use, to the extent necessary to protect the public health. In establishing any such regulation, the Administrator shall give appropriate consideration, among other relevant factors (1) to the necessity for the production of an adequate, wholesome, and economical food supply; (2) to the other ways in which the consumer may be affected by the same pesticide chemical or by other related substances that are poisonous or deleterious. . . ."[12]

Unfortunately, the meaning of this section is far from settled.

FDA interprets section 408 as permitting the use of carcinogens, so long as the risk from each individual chemical is not greater than 1 x 10^{-6}, or one cancer in a million persons exposed over a lifetime.[13] EPA reads the section 408 obligation to set pesticide tolerances "to the extent necessary to protect the public health" as granting the Agency broad discretion. EPA argues that section 408 is a risk-benefit standard, comparable to the standard for eliminating uses of pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).[14] The Agency believes that even levels of carcinogenic pesticides causing more than one cancer in the lifetime of one million exposed people can be lawful, so long as EPA identifies benefits which EPA determines "outweigh" the risks. Others, including public interest organizations, interpret section 408 to require EPA to limit pesticide residues to safe levels, and to prohibit all food uses of carcinogenic pesticides which pose risks at all detectible levels.[15]

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[11] Public Citizen v. Young, 831 F.2d 1108, (D.C. Cir. 1987).

[12] FFDCA, § 408(b), 21 U.S.C. § 346(b) (1982), emphasis added.

[13] NAS, supra, p. 94.

EPA recently permitted the use of the carcinogenic pesticide permethrin on raw tomatoes, while outlawing the processing of permethrin-treated tomatoes into tomato paste. The Agency side-stepped a blatant violation of the Delaney clause by mandating that tomatoes treated with the carcinogen could not be processed into foods which would concentrate the pesticide residue. But the Agency's action failed to protect consumers from the carcinogenic pesticide in the raw tomatoes. EPA's interpretation of section 408 and the 409 Delaney clause has resulted in an anomalous situation: fresh fruits and vegetables--the foods many consumers believe to be healthiest--may be laced with pesticides which would be unlawful on cooked, dehydrated or otherwise processed foods.

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[14] Environmental Protection Agency, "Regulation of Pesticides in Food: Addressing the Delaney Paradox Policy Statement," October 19, 1988, 53 Federal Register 41104, at 41106.

[15] See Nader v. EPA, No. 87-7103, (9th Cir., filed June 18, 1987) [whether FFDCA § 408 should be read to prohibit all residues of the carcinogenic pesticide daminozide (Alar).]

But consumers will not necessarily avoid carcinogenic pesticides even if they somehow manage to eat only the processed foods in which residue concentration occurs. Carcinogenic pesticides including daminozide, benomyl, dicofol, chlorobenzilate and the EBDCs[16] (ethylenebidithiocarbamates) are known to concentrate in some processed foods, notwithstanding the Delaney prohibition. Although the Delaney clause unequivocally prohibits the use of these carcinogens, EPA and FDA have simply ignored these violations of the law. These chemicals were registered decades ago, before their cancer-causing properties were identified. The National Academy of Sciences reports that EPA has applied the Delaney clause almost exclusively to new pesticides. The Agency has virtually ignored the clause's application to pesticides registered before 1972.[17] Last month, NRDC joined with the state of California, Public Citizen and the AFL-CIO to challenge EPA's failure to eliminate the food uses of pesticides which EPA has identified as carcinogenic and concentrating in processed foods.[18]

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[16] The most widely-used class of synthetic fungicides, used in the U.S. and throughout the world on fruits and vegetables.

[17] NAS, supra, pp. 40-41.

[18] State of California, Public Citizen, Natural Resources Defense Council and AFL-CIO Petition to Protect Public Health by Repealing the Food Additive Regulations for Seven Pesticides, Before the Environmental Protection Agency, May 25, 1989; and California v. Reilly, filed in federal district court in Sacramento, CA on May 25, 1989.

The federal agencies routinely assure the public that the food supply is safe. But data supplied by the pesticide manufacturers on the effects of those food-use pesticides that have been studied are ominous. Legal levels of residues from just 28 widely-used pesticides could cause cancer in as many as 6 out of every thousand persons.[19] Even if the tolerances were lowered by a factor of ten, or even a hundred, some of these agricultural chemicals would still pose cancer risks which exceed the government's standard for "negligible risk" of one in a million.

III. THE DELANEY CLAUSE IS VITAL TO THE PROTECTION OF OUR FOOD SUPPLY FROM CARCINOGENIC COLOR ADDITIVES, FOOD ADDITIVES AND ANIMAL DRUGS.

Many food industry representatives, as well as the current Food and Drug Administration, have sought to amend or repeal the three Delaney clauses in the FFDCA.[20] NRDC strongly opposes any such effort. An absolute prohibition on carcinogens is the appropriate standard for regulating food additives, color additives and animal drugs. We would vehemently oppose amendments, even if coupled with improvements to the regulation of pesticides, which undermine the strict Delaney prohibition on those carcinogenic substances used as food additives, color additives or animal drugs. Improved safety of the pesticides used in our food supply must not be achieved at the expense of increasing the hazards from other carcinogenic substances in food.

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[19] NAS, p. 89.

[20] FDA representatives recently told the House Energy and Commerce Committee: "We believe that this [negligible risk"] reasoning reflects good public policy and should also apply to other substances regulated by FDA that are subject to Delaney provisions." Testimony of John M. Taylor, Associate Commissioner for Regulatory Affairs, Food and Drug Administration, before the Health and Environment Subcommittee, House Energy and Commerce Committee, June 23, 1988, p. 4.

IV. S.722 IS ESSENTIAL TO IMPROVE THE SAFETY OF OUR FOOD SUPPLY.

A. S.722 REQUIRES PESTICIDE TOLERANCES TO POSE NO MORE THAN A NEGLIGIBLE RISK, INCLUDING FOR INFANTS AND CHILDREN.

The centerpiece of this bill is the requirement that pesticides used in food must pose no more than a negligible risk, which the bill defines as a rate of adverse human health effects of no more than one in a million. The bill requires that the EPA must ensure that "identifiable population groups (such as infants and other children)" are not subjected to a higher risk level. NRDC regards this provision as essential to public health protection. Average consumption estimates which are derived by dividing the total quantity of a food sold in the U.S. by the total U.S. population has very little relevance to the real consumption by individuals.

EPA's pesticide risk assessments and the resultant regulatory decisions generally assume an "average" diet. However, virtually every individual's diet deviates considerably from that of an average American's. Most people eat high quantities of certain foods and avoid other foods altogether. The consequence is that EPA's pesticide tolerances are designed to protect the theoretically average consumer--not the actual person who eats an apple, or two, a day. Consumers who eat higher quantities of any food than EPA considers to be average are not necessarily protected by EPA tolerances from developing cancers or other diseases caused by pesticides remaining on food. S.722 would require EPA to ensure that tolerances protect infants, children and other people who eat more than "average" amounts of foods treated with pesticides.

1. Explanation of Children's Enhanced Risk

NRDC demonstrated in our "Intolerable Risk" study that preschoolers have greater exposure to pesticide residues than adults. This is so because preschoolers eat more food, relative to their weight, and consume much larger quantities of fruit, which has a high likelihood of being contaminated with pesticides. Fruit comprises 20% of the adult diet and 34% of the preschooler's diet. Preschoolers eat six times as much total fruit, seven times more grape products and seven times more apples and apple sauce, relative to their weight, than adults. Apple juice is a particular favorite of children. The typical preschool child consumes almost 18 times as much apple juice and the typical toddler more than 31 times as much apple juice, relative to their weight, as the average adult woman.

Fruit is highly likely to contain pesticide residues. The 1987 FDA's food monitoring program found that 50% of all fruit samples had detectable levels of pesticides. This residue rate is higher than that of any other commodity and may significantly underestimate the full extent of residues because FDA's monitoring program does not routinely monitor for nearly half of the pesticide residues in food.

NRDC's analysis of exposure, based on a USDA study of food consumption by children and women, determined that relative to their weight preschoolers receive much greater exposure than adults to the majority of the pesticides analyzed in this report. The average preschooler receives more than five times greater exposure to the fungicide mancozeb, nine times greater exposure to the neurotoxic organophosphate azinphos-methyl and 12 times greater exposure to UDMH, the carcinogenic metabolite of daminozide, than adults. The typical preschooler receives four times greater exposure, on average, than adults to the eight carcinogenic pesticides evaluated. The youngest children receive the greatest pesticide exposure. Relative to adult women, toddlers receive more than eight times the exposure to mancozeb, 15 times greater exposure to azinphos-methyl and 18 times greater exposure to UDMH, than women.

B. S.722 REQUIRES THAT EPA ACCURATELY ASSESS EXPOSURE.

S.722 strengthens the federal pesticide regulatory program by requiring a more accurate assessment of exposure to pesticide residues as a prerequisite to a new pesticide tolerance. The bill requires that a pesticide legal limit take into account the other uses of the same pesticide on food and the other exposures to the pesticide the consumer experiences through the diet (such as through drinking contaminated water). These provisions are vital if the pesticide limits are to reflect the actual exposures experienced by our citizens.

The bill requires that exposures be evaluated on the assumptions that all commodities on which the pesticide's use is legal are treated with the pesticide, that the residue levels equal the pesticide tolerance level, and that exposure at the legal limit is likely to occur over a lifetime. These are reasonable assumptions which are necessary to ensure that the exposures of some members of society are not being ignored. The bill provides an exception whenever EPA has reliable data showing that less of the crop is treated and that the treated portion of the crop is distributed in a way which ensures that the risk is distributed evenly among consumers of the commodity. EPA is also allowed to calculate risk based on what they believe to be "actual residue" levels, but only if they then lower the tolerance to conform with the actual residue level.

EPA has not routinely lowered tolerances upon a finding that the legally permissible concentrations of pesticide residues would cause high risk of cancer or other adverse effects. EPA often dismisses these findings by stating that residues are normally below tolerance levels, but EPA does not concomitantly lower the tolerances to what it has declared to be the "normal" level. Consequently, people may unwittingly consume foods that, although legal, contain pesticide levels which EPA's data demonstrate to be unsafe.

Legal food should be safe food. Without prohibitively expensive chemical analyses of all food, consumers cannot identify which foods bear high residues and which have lower, safer concentrations of pesticides. Therefore, EPA should ensure that consumption of food with residues at the legal maximum is safe. EPA should perform risk assessments based on the assumption that pesticide residues will be present at the maximum legal concentration. If EPA, growers or the food industry believe that such a risk assessment overstates the risk, they should demonstrate that actual residues are lower and petition for a lower legal limit. This is how S.722 would function. The bill in effect requires EPA to limit risk to the level which they say results from the actual residues of the pesticide.

C. S.722 REQUIRES THAT EPA ESTABLISHES PRACTICAL METHODS OF ANALYSIS FOR ALL PESTICIDES, EXCEPT WHERE SUCH METHODS ARE NOT SCIENTIFICALLY FEASIBLE.

Pesticides should not be used on food if FDA cannot readily detect the residues in food. Without the ability to detect residues at reasonable cost, FDA cannot enforce EPA's tolerances and therefore cannot protect the public from pesticide residues in food. S.722 recognizes this fact and corrects the current anomalous situation in which dangerous pesticides are used on food which our government agencies cannot routinely find by their monitoring methods.

FDA monitoring for pesticides is inadequate to ensure that residues are legal, let alone safe. Of the 496 pesticides FDA has identified as likely to leave residues in food, FDA's routine analytical methods can only detect 203--only 41%.[21] Of the 105 pesticides which FDA considers to pose a moderate to high health hazard, only 58 (55%) are detectible using the FDA multi-residue methods.[22] Among the commonly used pesticides which cannot be detected by FDA's multi-residue methods are benomyl, daminozide, the EBDC fungicides and paraquat.[23] Twenty-six of the 53 pesticides identified by EPA as potentially oncogenic for the 1987 NAS report on pesticides in food cannot be detected by FDA's multi-residue method.

EPA should require that manufacturers of pesticides used on food develop practical methods for detecting pesticide residues. An analytical method should be considered practical only if the method: (1) reliably and routinely quantifies the level of residue in food with sensitivity sufficient to enforce the tolerance; (2) provides results in less than eight hours; (3) can be used in FDA labs with existing FDA laboratory equipment; and (4) costs no more than what is typically incurred by the FDA in using a multi-residue method. The bill would encourage the development of multi-residue methods for a wider range of pesticides. S.722 would greatly improve FDA's ability to enforce the pesticide tolerances.

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[21] GAO, Pesticides: Need to Enhance FDA's Ability to Protect the Public From Illegal Residues, October 1986, p. 33.

[22] Ibid, p. 36.

[23] Ibid, p. 39.

D. THE BILL REQUIRES DATA COLLECTION FOR ALL FOOD USES PESTICIDES WHICH HAVE NOT YET BEEN ADEQUATELY STUDIED.

EPA will be collecting important new data on the health and environmental effects of pesticides as a result of the 1988 amendments to FIFRA[24], but it is not clear when or whether EPA will use these data to reestablish tolerances at new levels which will truly protect the public health. S.722 requires the EPA to use this new data to rapidly set new tolerances which will be protective of our entire population.

Pesticides in food are legal up to the tolerance level. Yet residues are not necessarily safe at the tolerance level, or, as NRDC's "Intolerable Risk" report illustrates, even at levels well below the legal limit. This situation has occurred in part because most pesticide tolerances were set in the absence of reliable and complete data on the effects of long-term exposure. In fact, many existing tolerances were established by USDA prior to EPA's existence and were set with great deference to the economic interests of growers. Because the health effects of chronic low-level exposure were generally unknown, tolerance levels often only reflected residue levels resulting from growers' historical uses. Tolerances were routinely set high, so that crops subjected to the most frequent and most concentrated permissible pesticide treatments could legally be sold. EPA inherited these old tolerances from USDA when it was created in

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[24] Federal Insecticide, Fungicide and Rodenticide Act Amendments of 1988, Pub. L. 100-532, October 25, 1988.

1970. Unfortunately, many of these old, high tolerances still remain on the books.

Reregistration and reassessment of old pesticide tolerances are both desperately needed. Currently, petitioners must submit adequate data to support new tolerances. But EPA's process for obtaining data for already-registered pesticides is far less systematic. Although EPA has initiated chronic toxicity data call-ins for most food use pesticides[25], most of these pesticides are missing some crucial data, particularly in the area of residue chemistry. These data gaps have resulted in regulatory paralysis.

To illustrate this persistent problem, the Committee should consider the case of the EBDCs, the most widely-used group of fungicides registered in the United States. Both EPA's decision documents and the recent NAS Delaney report indicate high cancer risks for this class of fungicides.[26] The EBDC fungicides were registered in 1966 and 1967, and a special review of the cancer risks of the compounds began in 1977. In 1982 regulatory action was deferred in part because of incomplete information on exposure to the carcinogenic breakdown product, ETU. NRDC sued the agency, and we reached a settlement with EPA in 1984 when the

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[25] Testimony of Dr. John A. Moore, Assistant Administrator for Pesticides and Toxic Substances, EPA, Regulation of Pesticide Hearing, House Energy and Commerce Committee, June 8, 1987, p. 178. Also see 49 Federal Register 49544, December 20, 1984.

[26] EPA's decision documents indicate a lifetime dietary cancer risk of up to 4.9×10^{-4} (1 cancer in 2,000 persons exposed). NAS estimates for each of four EBDCs was similar. NAS, supra, p. 68.

Agency agreed to demand new data and to reassess the chemical before December 31, 1986. Registrants of these fungicides failed to comply with EPA's deadlines for submitting data. EPA now expects not to receive complete data until mid-1989.[27]

The case of the EBDCs is not unique. GAO reports that only approximately 50% of registrants submit EPA-requested data on old chemicals on time.[28]

Tolerance revision should occur rapidly when EPA learns of new or higher risks than were assumed when the legal limit was initially set as data comes in under in response to the 1984 food use pesticide data call-in[29] or the requirements of the 1988 FIFRA Amendments. S.722 would require appropriately swift action when new data is received.

E. S.722 REQUIRES THAT PESTICIDE INERT INGREDIENTS HAVE TOLERANCES UNLESS THEY ARE CHEMICALS WHICH ARE "GENERALLY RECOGNIZED AS SAFE".

The federal pesticide law distinguishes between active ingredients, which kill, repel or otherwise control pests, and so-called "inert" ingredients, substances which are used to dilute, propel or stabilize the active ingredient.[30] In many instances, the non-active ingredients are extremely toxic chemicals.[31] EPA has broadly exempted these "inert" ingredients from regulation under the FDCA. NRDC believes that current law requires EPA to set tolerances for these ingredients. However, we fear that litigation may be necessary to motivate EPA to set tolerances for these dangerous pesticide ingredients.

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[27] Testimony of Dr. John A. Moore, supra, pp. 151-153.

[28] "Data supplied by EPA from the [data call-in] tracking system indicate that about 47 percent of registrant responses to active ingredient data requirements (i.e., chronic toxicity data on the active ingredient) were overdue." General Accounting Office, Pesticides: EPA's Formidable Task to Assess and Regulate Their Risks, GAO/RCED-86-125, April 1986, p. 40.

[29] 49 Federal Register 49544, December 20, 1984.

S.722 requires EPA to revoke the food uses of dangerous "inert" ingredients unless they are "generally recognized as safe" or have a tolerance which ensures that they pose no more than a negligible risk. This provision would greatly enhance food safety. Because many so-called inert ingredients today are actually toxic chemicals, there may be instances in which the pesticide may pose excessive risks not because of the active ingredient but instead because of the substance used to dilute, propel, or stabilize the formulation.

Inert ingredients are generally not essential to the pesticide product. If a manufacturer wants to continue to use the active ingredient in or on food, the manufacturer should substitute an innocuous ingredient for the one posing a significant health threat. If an entirely innocuous ingredient cannot be found, the pesticide manufacturer must have the burden of testing the ingredients and demonstrating that at the tolerance level they will pose no more than a negligible risk in combination with the active ingredients. EPA should never allow residues of an inert ingredient to pose a significant health hazard.

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[30] The Federal Insecticide, Fungicide and Rodenticide Act, (FIFRA), 7 U.S.C. § 136(a) and § 136(m).

[31] EPA recently listed 57 inert pesticide ingredients of toxicological concern. 52 Federal Register 13305, April 22, 1987. Included on EPA's list were extremely dangerous chemicals, some of them restricted or cancelled by EPA, such as benzene, carbon tetrachloride, chloroform, formaldehyde, and mercury oleate.

F. THE BILL PROVIDES EPA WITH EXPLICIT AUTHORITY TO IMMEDIATELY REVOKE OR MODIFY TOLERANCES WHEN NEEDED TO AVERT AN "IMMINENT HAZARD."

Last year EPA Assistant Administrator Dr. John A. Moore testified before this Committee that under current authorities, EPA's revocation of a tolerance due to a registrant's failure to submit data promptly is labor-intensive and time-consuming. He suggested that revocation, when challenged by registrants, may take years.[32] Dr. Moore expressed the need for a provision in the law automatically revoking tolerances where data-submission deadlines are missed.[33] NRDC believes that food safety legislation should contain provisions automatically revoking tolerances if required data are not submitted in accordance with statutorily-defined deadlines. S.722 provides this necessary authority.

V. S.722 NEEDS STRENGTHENING IN ORDER TO ENSURE THAT PESTICIDES IN FOOD DO NOT ENDANGER PUBLIC HEALTH. NRDC WILL OPPOSE ENACTMENT OF ANY BILL WHICH WOULD ERODE THE PURELY HEALTH-BASED STANDARD OF S.722 OR WEAKEN STATE POWERS OVER PESTICIDES.

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[32] Testimony of John A. Moore, June 8, 1987, supra, p. 172.

[33] Testimony of John A. Moore, June 8, 1987, supra, p. 178.

A. NRDC URGES THE COMMITTEE TO ADOPT AN AMENDMENT TO REQUIRE THE ELIMINATION OF ALL PESTICIDES WHICH ARE HUMAN CARCINOGENS BY THE YEAR 2000.

Even though S.722 will help to reduce residues of carcinogenic pesticides in food, NRDC believes the bill should ultimately eliminate use of pesticides which are probable human carcinogens. Though the bill is an excellent interim measure, there are reasons to phase out all substances which EPA believes are likely to cause cancer in humans. First, the new tolerances which would be developed under the bill rely on risk assessment, which may understate the risk of certain pesticides. Furthermore, the bill does not ensure that cumulative exposures to carcinogenic pesticides in every American's diet is safe. Finally, the public needs assurance that even if federal agencies' implementation of the new law is no more diligent that their implementation of the old law, there will ultimately be a substantial reduction in the use of carcinogenic pesticides. Particularly given the ubiquitous exposures to other, non-pesticidal carcinogens--from radon and cigarette smoke to automobile emissions--NRDC considers it imperative that Congress take steps to minimize each person's exposure to substances which are carcinogens.

NRDC strongly urges this Committee to require EPA to revoke tolerances for all pesticides which authoritative federal agencies--such as the EPA, the National Cancer Institute, or the National Toxicology Program--identify as "probable human carcinogens." Alternative pest control methods must be sought for such substances. Pesticide manufacturers and growers will have no incentive to develop innovative crop protection processes as alternatives to carcinogenic pesticides unless there is a congressionally-mandated deadline for eliminating these dangerous pesticides. To allow for the time needed to conduct research in pest management to establish such alternatives, NRDC supports delayed application of such a provision for a number of years. Nevertheless, the American people deserve the assurance that by the year 2000 the foods they consume will not contain any pesticide which has been identified as a probable human carcinogen.

B. IT IS A PREREQUISITE TO NRDC'S SUPPORT FOR S.722 THAT THE CONGRESS MUST REJECT ANY CONSIDERATION OF ECONOMIC BENEFITS WHICH WOULD ALLOW PESTICIDES IN FOOD TO POSE GREATER THAN A NEGLIGIBLE RISK.

Tolerances should be set at safe levels. Benefits of the pesticide are irrelevant to the question of how much residue in food is safe. EPA currently interprets FFDCA section 408 as enabling the Agency to balance the risks of pesticide with the benefits of the chemical.[34] NRDC believes such an interpretation is unsupported by the statute, legislative history, or legal precedents. EPA testified before this Subcommittee last year and again earlier this month in favor of authority to grant tolerances for dangerous pesticides based on considerations of benefits.[35]

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[34] Testimony of John A. Moore, June 8, 1987, supra, p. 170.

Benefits considerations can become an enormous loophole to the strict regulation of widely-used but extremely dangerous pesticides. Those familiar with EPA's implementation of the FIFRA statute have witnessed EPA repeatedly cite economic benefits as the justification for continuing the registration of very hazardous pesticides. Benefits analyses appear to be developed ad hoc for the purpose of retaining current uses. Many of these analyses rely on unsubstantiated claims about the usefulness of the chemical. Seldom does the EPA consider that non-pesticidal crop protection strategies may serve as an alternative to pesticide use. Economic benefits to the pesticide industry or to gorwers should not be used to justify hazardous residues in our diets.

C. NRDC'S SUPPORT FOR S.722 IS CONTINGENT UPON THE CONGRESS' REJECTION OF ALL EFFORTS TO PREEMPT STATE AUTHORITY TO SET STRICTER PESTICIDE TOLERANCES.

Proponents of amendments which would preempt states' authority to set tolerances say that such amendments are needed to prevent a "crazy quilt" of conflicting legal requirements which complicate or interrupt interstate commerce of agricultural produce. Unfortunately, this assertion lacks an empirical foundation. Experience has revealed that states exercise their authority to set more stringent pesticide tolerances cautiously and only in compelling circumstances.

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[35] Testimony of John A. Moore, June 23, 1988, supra, p. 10-11; and Testimony of John A. Moore, Acting Deputy Administrator, Environmental Protection Agency, before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, May 15, 1989.

States have acted to set more stringent tolerances only when faced with extreme federal inertia in the face of ample evidence that public health was not adequately protected by federal tolerances. There are approximately three hundred pesticides approved for uses on food. Only two pesticides have been the subject of state efforts to tighten federal tolerances: ethylene dibromide (EDB) and daminozide.

In both instances where states set tolerances more strigent than the federal limits, many years of federal inaction or ineffective efforts preceded state action. In both instances compelling evidence was available on the basis of which state health authorities concluded that the risks from these pesticides were great, particularly for children. Both times the states tried to motivate the federal government to act and probably would have preferred swift and decisive federal action. The EDB and daminozide incidents did not stem from a surplus of conflicting and overlapping authorities to set tolerances. Instead, these events demonstrate the confusion and danger which result from the federal government's failure to exercise its authority to revise tolerances when new data reveal high risks.

1. Ethylene Dibromide (EDB)

Ethylene dibromide was first registered for food uses in 1948. EDB was used as a soil fumigant to kill nematodes as well as a post-harvest fumigant for grains and citrus. In 1956, on the basis of assumptions that no residues would remain on foods, EDB received an exemption from tolerance. The National Cancer Institute identified EDB as carcinogenic in 1974. In the late seventies, evidence established that contrary to expectations residues of EDB persist in food. EPA also obtained information confirming EDB's acute toxicity and adverse reproductive effects. Nevertheless, EPA's 1980 preliminary decision to cancel use of EDB was halted after Reagan Administration officials met with representatives of the food industry.[36]

In 1983 EPA took the first of a series of steps to limit use of EDB. EDB's use as a soil fumigant was suspended in September of 1983.[37] At the same time, EPA also began cancellation of the use of EDB as a grain and citrus fumigant, to become effective on September of the following year.[38] In February of 1984, uses of EDB on stored grain and grain milling equipment was suspended on an emergency basis.[39] Finally, in March of 1984, EPA announced a "phase out" over the next six months of EDB used to fumigate citrus.[40]

Despite these efforts to stop the domestic use of EDB, EPA still took no action to limit residues in food. Instead, Agency officials, including former Administrator Anne Gorsuch, convened numerous meetings with other Administration officials and representatives of food processing companies which are now spearheading this preemption effort in the Congress.[41] Although these food companies were able to persuade some Administration officials to delay action on EDB, they had less noteworthy success in certain states. NRDC believes that the drive to preempt the states was fueled by the frustration and surprise that certain food companies experienced when their influence in Washington, D.C. did not translate into power in the state capitals.

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[36] See Problems Plague the Environmental Protection Agency's Pesticide Registration Activities, House Committee on Government Operations, U.S. House of Representatives, 98th Congress, 1984.

[37] See 48 Federal Register 46228, September 28, 1983.

[38] See 48 Federal Register 46234, September 28, 1983.

[39] See 49 Federal Register 4452, February 3, 1984.

[40] See 49 Federal Register 17144, March 2, 1984.

EPA calculated the dietary risk from EDB residues in grains as 3.3 cancer cases per 1,000 individuals exposed.[42] This calculation did not include risk from dietary exposure to EDB residues in citrus or to EDB in drinking water. Actual residue testing done by some private and state laboratories indicated significant residues in many common foods. States began to exert their authority to protect citizens from exposure to EDB. Eight states required that baby food products have no detectable residues of EDB.[43] Some states also established tolerances for EDB in other foods. Finally, in April 1984, EPA established tolerances for EDB in foods--but the federal limits were higher than those already set by some states.

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[41] See Problems Plague the Environmental Protection Agency's Pesticide Registration Activities, House Committee on Government Operations, U.S. House of Representatives, 98th Congress, 1984.

[42] Environmental Protection Agency, Ethylene Dibromide: Position Document 4, September 1983, page 69.

[43] California, Connecticut, Florida, Maine, Massachusetts, Michigan, New York and Texas.

2. Daminozide and UDMH (Unsymmetrical Dimethylhydrazine)

The Agency's experience with daminozide (Alar) is not dissimilar to the EDB story. Daminozide, a growth regulator, was first registered for use on apples in 1969. Daminozide is primarily used on apples, but it is also used on peanuts, cherries, grapes and other fruits. Apples treated with daminozide ripen more slowly and are less likely to drop before harvest, are denser and store better, and have an enhanced color. However, five separate pre-1985 studies demonstrated the carcinogenicity of daminozide and its metabolite, unsymmetrical dimethylhydrazine (UDMH). Toxicological evidence suggested that UDMH may be an even more potent carcinogen that daminozide itself. New data also revealed that the transformation of daminozide into UDMH is accelerated by heating, as occurs during cooking or processing apples into applesauce and apple juice.

Because of the accumulating evidence of the carcinogenic potential of daminozide and UDMH, by 1985 many states were concerned about the danger posed to infants and children who consume processed apple products such as apple juice and applesauce at disproportionately high levels compared to adults. Several states also recognized that children may be even more vulnerable than adults to carcinogenic exposure because of their incompletely developed immune systems and the greater likelihood that they will live beyond the latency period necessary for the development of cancers. Children's more rapid rate of cell development may also make them more susceptible to carcinogens.

Although the first study demonstrating a cancer risk was performed in 1973, there was no hint of regulatory action on daminozide until seven years later. Then in 1980 EPA initiated a series of closed-door meetings with the sole manufacturer of daminozide, Uniroyal.[44] In September 1985, EPA proposed to stop any further food uses of daminozide. Uniroyal insisted that the carcinogenicity studies were flawed, although the flaws noted were ones which would normally understate the risk. However, Uniroyal never initiated its own carcinogenicity tests on their product. EPA's Scientific Advisory Panel on September 27, 1985 overturned EPA's staff recommendation to cancel daminozide. EPA granted Uniroyal four more years in which to conduct new cancer studies.

The chief public health officials in the states of New York and Massachusetts wrote to EPA in 1985 to register their concern about the risk from daminozide, particularly for children. These health officials recommended restriction or cancellation of food uses of daminozide.[45] However, in January 1986, EPA reversed its position and continued existing uses of daminozide, pending further study.

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[44] In accordance with a settlement obtained with EPA by NRDC and the AFL-CIO, this practice of secret consultations with pesticide manufacturers has been discontinued. Settlement agreement in NRDC et al. v. Ruckelshaus, No. 83-1509, (D.D.C., September 20, 1984.)

[45] Letter of Dr. Ballus Walker, Commissioner, Department of Public Health, The Commonwealth of Massachusetts, to Mr. Steven Schatzow, Director, Office of Pesticide Programs, U.S. Environmental Protection Agency, January 16, 1985; Letter of (continued...)

EPA also proposed on April 16, 1986 to reduce the tolerance for daminozide-treated apples from 30ppm to 20ppm.[46] Massachusetts has taken measures to minimize exposure to daminozide.[47] Inordinate delays at the federal levels led other states, including Maine and New York, to consider regulatory action to protect public health from daminozide.[48]

On February 1, 1989, based on data from the halfway point in a new Uniroyal UDMH study, EPA announced concern about the occurrence of statistically significant increases in unusual blood vessel tumors in mice. From this study EPA estimated an alternative cancer potency factor which is lower than that

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[45](...continued) David Axelrod, M.D., Commissioner of Health, State of New York to Dr. John Moore, Assistant Administrator, Office of Pesticide Programs, U.S. Environmental Protection Agency, October 25, 1985.

[46] See 51 Federal Register 12889, April 16, 1986. The rule implementing the tolerance modification became effective on January 16, 1987. See 52 Federal Register 1909, January 16, 1987.

[47] Action Levels for Poisonous or Deleterious Substances in Food, Mass. Admin. Code Tit. 105, 515.000 (1986).

[48] State of Maine Department of Agriculture, Notice of Agency Rulemaking Proposal, Daminozide/UDMH: Acceptable Residue Levels in Heat Processed Foods, May 28, 1986. Testimony of Ms. Marilyn DuBois, Chief, Bureau of Pesticide Management, New York Department of Environmental Conservation, before the Department Operations, Research and Foreign Agriculture Subcommittee of Agriculture Committee, U.S. House of Representatives, June 10, 1987.

derived from the pre-1985 studies.[49] The new Uniroyal study further corroborates carcinogenicity findings from pre-1985 laboratory tests, demonstrating once again that the earlier studies provided a reasonable basis for estimating the cancer risk from UDMH.

3. States have Rarely and Cautiously Exercised their Authority to set more Stringent Tolerances.

States have never used their authority to set distinct tolerances where the federal government has already set adequately protective limits for permissible pesticide residues on foods. State authority has been used judiciously and only after protracted delays at the federal level. No state has used its tolerance-setting authority to interfere with interstate commerce or to block the importation of produce from other states. Instead, divergent tolerances have been based on weighty evidence that the dangers of EDB and daminozide were being inadequately addressed by EPA. State power to set tolerances must be preserved to enable states to protect their citizenry when the federal government cannot or will not respond to pesticide problems.

VI. CONCLUSION

NRDC applauds the Chairman for this important piece of legislation to ensure that pesticides in food are safe. Legislation of this kind is urgently needed to restore public confidence in our federal programs to protect our food supply. We urge the Committee to challenge those who maintain that this bill would result in enormous losses to agriculture. NRDC believes that there is no evidence to justify such claims. This bill does not require the banning of pesticides whenever they pose a risk. Instead, the bill wisely requires that residues of dangerous pesticides must be limited to a level which is safe for all members of society. This bill would require EPA to phase out the uses of pesticides only when the chemicals are so dangerous that they cannot be used in agriculture effectively at levels which pose a negligible risk to the public. The American public is demanding a vastly safer food supply. We hope to work with this Committee ensure that the public's demand is heeded.

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[49] NRDC requested, but was not given, EPA's revised UDMH cancer potency factor before we released our report.

National Coalition Against the Misuse of Pesticides
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PREPARED STATEMENT OF THE NATIONAL COALITION AGAINST THE MISUSE OF PESTICIDES

Mr. Chairman and members of the committee. Thank you for the opportunity to address you today on a problem of extreme importance to the public and our membership --the safety of our food supply.

I am Jay Feldman, National Coordinator of the National Coalition Against the Misuse of Pesticides (NCAMP). NCAMP, founded in 1981, has been working with local groups and people across the United States and around the world in an effort to ensure safety from pesticides in our food, water, land and air. Our membership, including those living in urban and rural areas, on and off the farm, is composed of people, including approximately 200 community-based groups in nearly every state, with concerns about a range of pesticide-related issues, who seek to reduce and where possible eliminate pesticide exposure while promoting alternative methods of pest control which do not rely on these toxins.

I appear here today on behalf of people across this country who applaud you for taking the time to roll up your shirt shelves and grapple with the pesticide poisoning problem --an issue that has been known to be controversial, with many intransigent players who have a vested interest in things simply not changing (or things not changing significantly). Unfortunately, our message today is not without criticism and, because of limited time and space, we must focus on the "negligible risk" standard of safety, the centerpiece of S. 722, *Food Safety Amendments of 1989*, because we believe that it is this very standard which will continue to undermine the safety of the U.S. food supply.

The "negligible risk" standard must be explored in great depth because everything else in the legislation flows from the very standard of safety embodied or enshrined in it. "Negligible risk" is a standard which must be challenged for scientific, agricultural, political and judicial reasons, a standard which will exacerbate the public's growing and justifiable lack of confidence in the safety of the food supply. The public does not want to be lulled into a false sense of security, only to wake up in another ten years, to find that the nation's cancer epidemic is still robbing families of their young loved ones at a rate of one in four premature deaths, or worse has climbed even higher.

Having worked on pesticide issues now for over a decade, I can tell you that public concern has grown steadily and continues to grow. Even before the recent media focus on Alar™ (daminozide), public concern had been documented in numerous polls, such as a Harris Poll taken in late 1988, which found that 84 percent of those polled would like access to food grown without pesticides. Again, even before the Alar™ controversy, the Food Marketing Institute consistently found an average of 75 percent polled identifying pesticides in their food as a serious hazard. The U.S. Environmental Protection Agency (EPA), in its 1987 report *Unfinished Business: A Comparative Assessment of Environmental Problems*[1], identifies pesticide residues in food as one of the nation's three most serious public health threats, next to worker exposure to chemicals and radon.

The issue today is not whether there is a problem –numerous government and independent reports have highlighted the problem,[2] the issue is what are we going to do about it. We do not believe that the issue must inevitably polarize those who grow food from those who eat food, because our coalition is testimony to the fact that growers and eaters agree –the food supply must be safe. We will see polarization between consumers and vested interests that use, promote or in some way are invested in continuing status-quo patterns of pesticide use.

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[1] U.S. Environmental Protection Agency, *Unfinished Business: A Comparative Assessment of Environmental Problems*, Washington, D.C., 1987.

[2] U.S. General Accounting Office (GAO), *Pesticides: EPA's Formidable Task To Assess and Regulate Their Risks*, Washington, D.C., GAO/RCED-86-125, 1986; GAO, *Pesticides: Need to Enhance FDA's Ability To Protect the Public From Illegal Residues*, Washington, D.C., GAO/RCED-87-7, 1986; GAO, *Pesticides: Better Sampling and Enforcement Needed on Imported Food*, Washington, D.C., GAO/RCED-86-219, 1986; National Research Council, *Regulating Pesticides in Food: The Delaney Paradox*, Board on Agriculture, National Academy Press, Washington, D.C., 1987; Mott, L. and K. Snyder, *Pesticide Alert: A Guide to Pesticides in Fruits and Vegetables*, Sierra Club Books, San Francisco, CA, 1987; Epstein, S.S., "Losing the War Against Cancer: Who's To Blame and What To About It," *The Ecologist*, 17(2):91-99, 1987; Epstein, S.S. and J. Feldman, "Opening the Door for Carcinogens: Assaults on Nation's Food-Safety Laws Multiply," *Los Angeles Times*, February 27, 1989, Part II, p.5; Price, P., *The Invisible Diet: Gaps in California's Pesticide Residue Detection Program*, Joint Publications Office, State Capitol, Sacramento, CA, 1988; Feenstra, G., *Who Chooses Your Food?*, California Public Interest Research Group, Los Angeles, CA, August, 1988; Mott, L. with M. Broad, *Pesticides In Food: What the Public Needs To Know*, Natural Resources Defense Council, San Francisco, CA, March, 15, 1984.

If the question before us is how are we going to make our food supply safe for everyone, then we must consider what results may or may not follow from implementation of a program such as that detailed under S. 722. The most important element to recognize, we believe, in analyzing the bill is that the "negligible risk" standard is based on still imperfect methods of predicting risk, collectively known as risk assessment. It is the inadequacies of these predictive tools that require our critical examination in order to evaluate the validity of the concept as a whole.

If you find, as we have, that the predictive value of risk assessment tools vary significantly, then we ask whether there is adequate justification for public exposure to poisons. In other words, if the very tools you are using to measure risk are flawed, so that there is serious doubt that the "negligible risk" standard proposed in S. 722 is as protective as you think it is, then on what basis can you justify to the public that the risks are inconsequential, particularly to a subgroup of the general population, like children or elderly, that is at highest risk. Moreover, if you allow the continued use of pesticides resulting in "negligible risk," despite the flawed formulation of the concept, on what basis can you exempt these pesticide uses from an essentiality review, with required studies and facts supporting the assumed necessity of the various registered pesticide uses.

It is one thing to establish a scientifically pure negligible risk level, or as the agri-chemical industry has called it a "so-what level," and allow the introduction of toxic pesticides into our food supply up to that level. It is quite another to accept the introduction of toxins into the environment and food supply up to an ill-defined and ill-controlled "negligible" standard, when alternative methods of food production exist that do not subject the public to that level of hazard.

Mr. Chairman, I do not believe that it is your intention to create a clean-up standard in S. 722, cleaning up after past mistakes to a level achieved by the best available technology. Instead, we are talking about the establishment of a standard by which a society prohibits the purposeful introduction of poisons into the food supply and rejects the unproven assumption that these poisons are necessary to a food production system yielding affordable food prices.

Below, we provide you with an analysis of critical problem areas with S. 722.

I. "Negligible Risk" Relies on the Uncertainties of Risk Assessment

NCAMP's premise: **The "negligible risk" formulation and its reliance on risk assessment modeling is not an adequate predictive tool to measure the potential hazards to people ingesting known poisons (e.g. carcinogens).**

a. The act of generating risk assessment numbers cloaks our ignorance of the risks with a false authority and objectivity. In order to calculate risk with authority, it is necessary to understand the cancer process thoroughly. Science does not. Since *cancer is a collection of diseases, most of which proceed by mechanisms which are not at all understood*, and probably not all alike, it is impossible to define a safe level of exposure. If one proposed mechanism of chemical carcinogenesis is in fact true, that some carcinogens act by altering genes and that cancer results when the damage is not reversed (a process whose efficiency probably varies from person to person), then theoretically, for some individuals there may be no safe level of exposure. Nothing has appeared in the scientific or regulatory literature to our knowledge which can argue against the traditional conservative interpretation that zero exposure is the only safe exposure. This is especially likely to be true since exposure to numerous carcinogenic chemicals at once seems to be everyone's destiny from the moment of conception.

b. Even conservative models are far too crude to provide absolute assurance of safety. Depending on the assumptions and models that are used, it has been found that calculated risks can vary by orders of magnitude. Even conservative models may not be as conservative as is commonly advertised. For example, let us look at two popular risk assessment models commonly referred to as "conservative."

> 1. The *One-Hit model* assumes that a single exposure to a carcinogen may result in a tumor. It has become accepted practice to use animal cancer bioassays in which animals are exposed at doses that approximate the animal's maximum tolerated dose. This is done in order to maximize the likelihood of a positive effect, using experimental animal group sizes that are manageable logistically and economically. Central to predicting the toxic effects of a substance is the process of generating a graphical dose-response curve. The shape of such a curve may vary from chemical to chemical and even for a single chemical is not likely to be linear over its entire range. However, scientists plotting tumor incidence against dose of the putative carcinogen are plotting data points relevant to the high end of the curve, where doses are large. In point of fact, the validity of extrapolation down to low doses is not easily verifiable, and may not accurately predict the shape of the curve at that end of the scale.
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> For the *One-Hit model* it has generally been assumed (because of mathematical proofs) that tumor yield graphed against dose will be linear in the low-dose range. This model, by the way, has been widely considered to be our most conservative model, and it is the model that EPA uses. In fact, a recent review (Bailar, et al., 1988)[3] indicates that it may not be as

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[3] Bailar, J.C., et al., "One-Hit Models of Carcinogenesis: Conservative or Not?," *Risk Analysis*, 8(4):485-497, 1988.

conservative as is popularly assumed. These researchers reviewed National Toxicology Program data from 1212 bioassays on 308 chemicals that had been tested at three doses. The extrapolated curve generated by using the *One-Hit model* equation was compared with actual tumor incidence found at the mid-range dose in the animal study in question. It was found that in a small percentage of cases, the mathematically-generated curve deviated significantly from the actual animal bioassay results. This occurs more frequently than expected by chance, resulting in significant under-estimation of risk by this supposedly extremely conservative technique.

2. One of the very first low-dose extrapolation models used for risk estimation was the *Mantel-Bryan* model. According to A.W. Hayes, "...the *Mantel-Bryan* procedure is regarded as one of the pioneering techniques in low-dose risk estimation...[but it] often leads to a poor fit to the observed, experimental data, which would certainly raise questions about its suitability for low-dose risk estimation. Furthermore, the assumption of an underlying log-probit [tumor yield plotted against the $\log_{10}$ (dose)] distribution **has no particular biological justification** [our emphasis], since there is no mechanistic model of carcinogenesis that logically leads to its use. In addition, the probit model...will typically generate an estimate of low-dose risk that falls well below any produced by. . .competitive techniques in spite of the fact that those who advocate its use often characterize it as a conservative procedure."[4]

c. **Current methods of estimating both carcinogen potency and exposure ignore the contribution of a number of factors likely to be relevant to actual human exposure conditions.** Cancer risk is calculated as the product of [potency] times [exposure]. The potency of a carcinogen is derived by calculating the slope (the pitch or steepness) of the curve graphed by plotting tumor yield against dose in animal bioassays. These slopes, which EPA calls Q*-values, may be derived from a series of carcinogenicity bioassays and averaged to get an overall potency figure. The artificiality of this process is especially troublesome when experimental data do not correspond well to linear dose-response models, for example with many Class C (possible human) carcinogens. If no Q* is easily calculable, EPA may not be able to do a risk assessment, which explains why many chemical manufacturers agitate to get their chemicals classified Class C since the stigma of "carcinogenicity" attached to their products is lessened.

But is this all there is to calculating potency? Clearly not. Potency is alterable by a host of external factors. As Maugh stated in a 1978 review, "Significant differences in the observed potency of carcinogens in laboratory animals can be obtained, for example, by exposing the animals to chemical agents that stimulate or depress drug-metabolizing enzyme systems; by modification of the animals' diet; by changing the hormonal balance of the animals; and by stressing the animals in various ways, such as by increasing the number in a cage."[5] Most importantly, the influence of multiple chemical exposures is an important issue that current mathematical models are too crude to address.

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[4] Hayes, A.W., *Principles and Methods of Toxicology*, Raven Press, New York, NY, 1984.

d. **A risk assessment that incorporates sensitive populations can still allow for a disproportionately high risk in some groups.** Exposure calculations are just as artificial as potency estimates and can be derived in several ways, depending on the quality of the pesticide residue data base. Regulators can assume, if actual residue data do not exist, that residue levels approach tolerance levels and appear on 100% of a given crop for which the pesticide is registered. This is recognized as an extremely conservative approach, of course. Nevertheless, whatever the basis of the calculations, dietary exposure estimates tend to generalize risk over an "average" situation or population, away from the consideration of particular situations and individual sensitivities.

This is dangerous over-simplification, since the simple inclusion of exposure figures for sensitive sub-populations within the overall average exposure calculation does not, in fact, address the particular hazard that a sub-population might face, rather, it obliterates it from conscious consideration.

Another orientation is more appropriate. As stated by Hattis, 1989, "Should the analyst take pains to uncover and disclose the distribution of the risk among the population? A 10^{-6} risk of death from a specific hazard for an aggregated group might translate into 10^{-2} for a particularly at-risk subset--Holdren (1982)[6] cites possible differences in the distribution of risk between rich and poor, the medically susceptible and the population as a whole, and between those who have a voice in the acceptance of risk and those who do not."[7]

Therefore, it is no trivial question to wonder why S. 722 contains no language to describe the kind of models to be used for risk calculations that will effectively assure the public that "negligible risk" of cancer will really be all that negligible.

e. **Lifetime exposure models tend to minimize the reality of short-term**

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[5] Maugh, T.H., "Chemical Carcinogens: How Dangerous Are Low Doses?," *Science*, 202:37-41, 1987.

[6] Holdren, J., "Energy Hazards: What To Measure, What To Compare," *Technology Review*, April, 1982, pp. 33-39, 74-75.

[7] Hattis, D. and J. Smith, What's Wrong With Risk Assessment?," *Biomedical Ethics Reviews*, in press.

exposure hazards and differences in lag-times to cancer development among populations. It is common to speak of cancer as a disease of old-age, and to generalize all cancers as diseases that only manifest themselves after a considerable lag-time. It is certainly true that many cancers do not appear until much time has passed, but it is not true that all do. Retinoblastoma, for example, is a tumor of the eye which is almost always diagnosed in children under the age of two. Obviously, a long lag-time does not elapse between the triggering event and development of the tumor in this disease. This situation might be generalized to many childhood cancers. However, the same principle may also operate in the development of certain adult cancers, especially blood tumors.

Most epidemiological investigations follow a population for a long period of time, certainly the proper conservative approach, but researchers have occasionally noted that effects might have been picked up earlier than the traditional 20 or 30 year follow-up period. For example, see a recent study of the relationship between agricultural chemical use and rural cancer (Stokes and Brace, 1988), in which the authors note: "Our results indicate that significant associations may be found within shorter [than 20-year lag] periods."[8]

Current risk assessment methodologies do not consider the possibility that certain cancers may require less of a lag-time to become manifest, nor is the possibility that the timing of exposure may be important. The idea that exposure to carcinogens in childhood may place adults at greater risk of developing cancer later life was addressed at some length in the Natural Resources Defense Council report on pesticides in food, *Intolerable Risk.*[9]

Another common assumption in risk assessment is that when tumors in rodent bioassays are found only at the end of a rodent's lifespan, the risk to humans is probably going to be less, since the theory is that the carcinogen in question triggers the development of only end-of-lifespan tumors. This may be an erroneous assumption. A series of papers by a German investigator, Dietrich Schmahl of the German Cancer Research Center in Heidelberg, report data on time-to-tumor comparisons among animal species which have life spans of varying lengths. His work indicates that when exposed to equivalent doses of a carcinogen, the time-to-tumor from species to species is the same. In other words, if a cat and a rat are given the same doses of a carcinogen, it will take roughly the same amount of time for the cat to develop tumors as the rat, but this means the cat will develop tumors earlier in its life span than did the rat. The implications for extrapolating risk predictions from rodents to humans may be that a human's greater life span argues for less tolerance of unnecessary exposures to carcinogens, not more.[10]

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[8] Stokes, C.S. and K.D. Brace, "Agricultural Chemical Use and Cancer Mortality in Selected Rural Counties in the U.S.A.," *J. Rural Studies*, 4(3):239-247, 1988.

[9] Sewell, B.H. and R.M. Whyatt, *Intolerable Risk: Pesticides in Our Children's Food*, Natural Resources Defense Council, New York, NY, February, 1989.

f. **Recognition and consideration of the limits of scientific certainty represents the true "worst-case" analysis, but this is rarely admitted.** The National Environmental Policy Act (NEPA) [40 CFR 1502.22] sets out the rules governing the preparation of Environmental Impact Statements. As noted in a review by O'Brien, 1988, NEPA directs federal agencies to consider the impacts of information that is not yet known or is unavailable, information which may nevertheless be "essential to a reasoned choice among alternatives." Furthermore, NEPA states that, "If the Agency proceeds, it shall include a worst case analysis and an indication of the probability or improbability of its occurrence."[11]

In other words, the process of fully addressing what could go wrong if the elaborate, elegant mathematics simply do not turn out to be predictive of reality, frees society from complacent acceptance of a non-optimum status quo, and becomes a driving force for the search for alternatives.

g. **Differences in professional judgement cloud the issues.** It is a well-known fact that very few pesticides are well tested for possible adverse effects on the environment or public health. With the passage of the 1988 amendments to the Federal Insecticide, Fungicide and Rodenticide Act (known as "FIFRA-Lite" because of the range of critical issues that were not addressed), it is to be hoped that over the next decade or two EPA will finally be demanding, receiving and reviewing a great deal of data to redress this decades-old problem. However, one problem has still not been addressed. The data used to register pesticides continues to be generated by registrants, it is still not peer-reviewed, and it is still not generally available to independent scientists or the public. It is a fair question to wonder whether EPA scientists, or anybody's scientists, should have total control over the physical data and its interpretation. Recently, State Senator Nicholas Petris (D-CA) challenged the accuracy of EPA's data evaluation program, making public a California Department of Food and Agriculture (CDFA) report citing many differences of opinion between CDFA scientists and EPA evaluators of the same pesticide registration data.[12] Some of these differences of opinion were quite serious (e.g., a rat teratology study that did not contain a teratology section.) CDFA reviews found disparities in 58 of 99 active ingredients, or 59% of the time, while EPA ascribes most of the disagreements to "differences in professional judgement." A docket is to be created detailing just what these consist of, and the specific responses of EPA scientists, but it is not yet available for review.[13]

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[10] Personal communication with Dr. William Lijinsky, Frederick Cancer Research Center, Frederick, MD.

[11] O'Brien, M., "Quantitative Risk Analysis: Overused, Under-examined," *Journal of Pesticide Reform*, 8(2):7-12, 1988.

[12] Letter from California State Senator Nicholas Petris to Acting Administrator John Moore, October 25, 1988.

EPA itself admits that scientists are not free from the capacity for error, nor do scientists always agree on data interpretation. The point is that S. 722 grants EPA broad authority to establish safety standards despite a poor track record and outstanding "differences in professional judgement." The Petris controversy serves to remind us that the EPA review process is not an infallible base on which to build any kind of a cancer risk calculation, much less any other kind of risk calculation.

II. Implicit Benefits are Being Falsely Attributed to Poisons

NCAMP's premise: **Allowing the poisoning of food up to the "negligible risk" level, implies a pesticidal benefit that is never calculated, despite the availability of alternative non-chemical methods of food production. One of the underlying problems with risk assessment, as it is being promoted in S. 722, is its use as a substitute for asking whether we need a particular pesticide in the first place.**

We appreciate, Mr. Chairman, your intention to set the regulation of pesticide residues in food on a firm health-based footing. It is clear that neither of us sees any merit in adopting the profits versus public health standard contained in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

We believe that it is especially inappropriate to introduce any level of a poison, particularly a cancer-causing one, into the food supply with an assumption that it has benefits. The only reason that federal law allows the introduction of pesticides into the environment is because of a presumed benefit, a concept basic to EPA's implementation of the FIFRA. We do not believe that the safety standard, as it is proposed in S. 722, does anything to change the nature of this assumption, as it is currently implemented by EPA. The bill does indeed accept the assumption that the pesticide in question has a benefit, or has a market. NCAMP believes, however, that it is inappropriate to adopt the benefits assumption when it comes to the introduction of poisons into the environment and food supply.

EPA's, and thus S. 722's, assumed pesticide benefits analysis is simple: If a manufacturer thinks he can make a go of it and the pesticide presents nothing more than a "negligible" cancer risk, then the poison can be marketed. In referring to its interpretation of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), EPA has said,

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[13] Letter from EPA Acting Deputy Administrator John Moore to California State Senator Nicholas Petris, March 3, 1989.

> "If a pesticide's use would pose no risk or only a negligible risk, the pesticide's use would be approved under both Acts without any particular scrutiny of benefits. This has for some time been EPA's practice with respect to decisions on pesticides that pose only non-cancer risks, and with respect to decisions under FIFRA and under FFDCA section 408 on pesticides that may pose cancer risks. (EPA has assumed that an applicant's [pesticide manufacture's] willingness to expend the sums required to obtain registration of a pesticide, in the expectation of recovering those sums by sales of the pesticide, indicates that the pesticide's use will yield benefits that are greater than negligible.)"[14]

If the reason society allows the introduction of poisons into the food supply is simply to provide market opportunities for enterprising entrepreneurs, then the laws needs to be redrafted to reflect this. However, if we as a society allow the introduction of known hazards such as carcinogens into an environment because we attribute or imply benefits to these toxins, then our current implementation and its continuation under S. 722 is flawed for a number of basic reasons.

- *First*, in most cases there exist alternative methods of pest management that can be accomplished with less toxic or non-toxic means. Therefore, the risks, no matter how they are defined, and the pesticide are not necessary.

- *Second*, the pesticide does not often perform as is intended in the long-term (as short as two seasons) because of resistance, now being seen in 447 insect species and related organisms, 45 weed species, 100 plant pathogens and 3 rodent species.

- *Third*, often the pesticide use is simply contributing to unnecessary production, which is the case with surplus corn and wheat, doused with 110 million pounds of pesticides in 1986.

- *Fourth*, pesticides are often used for cosmetic purposes, some estimates being as high as 40 to 60 percent of pesticides.

- *Fifth*, pesticide use often creates secondary pest infestations, creating pest problems that did not previously exist, rationalizing additional pesticide use.

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[14] 53 *Federal Register* 411050, October 19, 1989

It is inappropriate to assume pesticide benefits and allow any pesticide use that is essentially unnecessary. It is particularly inappropriate to assume pesticide benefits and allow contamination up to a defined safety threshold, "negligible risk," that is flawed.

III. Existing Law Has Not Been Enforced

NCAMP's premise: **Existing law can be improved to provide the public with a safe food supply, however the repeal of the *no additional cancer,* or "no induction of cancer," standard of the Delaney Clause and replacement with a "negligible risk" standard represents a severe blow to our national food safety goal. Legislation should seek to reaffirm the *no additional cancer* goal, rather than repeal it. The failure of EPA to implement this goal justifies its strengthening, not its repeal.**

The basic question in front of us is how best to respond to the public's desire for a safe food supply. The question is not whether S. 722 affords the public a safer food supply than the EPA's current non-enforcement of existing law. The question is whether the changes in the law would afford us the safety people would like. The answer is that S. 722 would not afford people the safety that is desired.

The reasons we are facing food safety concerns today are at least twofold. One, EPA has not been enforcing the food safety laws. Two, the food safety laws need strengthening to ensure EPA and FDA enforcement.

a. The distinction between raw and processed foods under FFDCA. Under existing law, we believe EPA has the duty to prohibit the introduction of cancer causing pesticides in processed food, and practically speaking, in most raw agricultural commodities. Despite a distinction in FFDCA between raw (section 408) and processed food (section 409), with a stronger *no additional cancer* standard applied to processed food, the practical implementation of this policy would protect the public from exposure to cancer causing pesticides in the food.

Prior to adoption of EPA's "negligible risk" standard, EPA's policy, as stated, maintained "...[S]ince there is no practical way to assure that the raw agricultural commodity at issue will not be processed, the Agency generally does not grant a section 408 tolerance for residues of the pesticide on a raw agricultural commodity in a situation where an associate section 409 food additive regulation is needed but cannot be issued." It is our position that EPA has a duty to apply this interpretation to new as well as older pesticides when the agency obtains data it did not have upon its original registration.

b. The application of section 408, FFDCA to raw foods. EPA fails to enforce the public health standard of section 408, despite litigation which clarified its responsibility. NCAMP sued EPA on their application of this standard when it allowed the importation of mangoes with levels of ethylene dibromide (EDB) which were banned in the U.S. In effect, EPA created an exemption for imported mangoes, based on an argument that the law provided the authority to consider factors other than those strictly related to public health, such as foreign economic harm. In its defense, the agency maintained that the statute provides the agency with broad discretion to determine what factors are "relevant" to formulation of a tolerance. However, according to the court decision:

> The more natural reading of the statutory phrase, "other relevant factors," in section 346a(b) is that EPA can consider only factors related to protection of public health. It is, after all, "the public health" that EPA is charged with protecting through "regulations establishing tolerances." . . .[T]he provision clearly mandates that health factors and issues of foreign impact related to the health of U.S. consumers be at the forefront of EPA's deliberations. . . . We have not occasion to say whether the administrative record could support a decision that the economic impact of a zero tolerance could be so severe as to threaten "the public health" --for example, by disrupting the country's mango supply, which could raise concern about the need for an "economical food supply," or encouraging the illicit infiltration of fruit fly-infested mangoes, which could similarly pose a risk to the "adequa[cy] and "whole-some[ness]" of the food supply. We hold only that EPA has not established any such linkage, nor under settled principles can counsel's *post hoc* rationalizations cure this deficiency.[15]

While court interpretation is not equivalent to the protection provided by the *no additional cancer* Delaney clause, it clearly is not the same, less protective risk-benefit standard contained in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as EPA repeatedly characterizes it. In fact, EPA, given its section 408 mandatory duty under existing law in setting tolerances on raw agricultural commodities without a processed counterpart, is required to make a showing that the only way it can protect public health is by allowing the use of carcinogenic pesticides. EPA would have to show the public that to do otherwise, would threaten public health by threatening an "adequate, wholesome and economical food supply."

EPA has ignored its mandatory duty. EPA has not enforced the existing law. EPA blatantly ignores its responsibility when it assumes that the marketplace determines benefits of "negligible risk" pesticides. Similarly, S. 722 ignores the government's responsibility to protect public health when it builds a food safety standard on a flawed "negligible risk" standard and allows these pesticides on the market on the basis of entirely assumed benefits.

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[15] NCAMP v. Thomas, 809 F.d 875 (D.C. Cir. 1987)

IV. Enforceability of the Standard is Highly Questionable

NCAMP's premise: **The creation of a standard that cannot be challenged by the public through judicial review gives an agency carte blanche to contaminate. Because the courts typically defer to EPA's judgement on "scientific" issues, such as calculations of risk, the public, under S. 722, will be unable to challenge EPA's "scientific judgement." Given the uncertainty of the science, the range of EPA judgments and poor past performance, the public is left unprotected.**

With all the problems mentioned above that the public has had winning enforcement of the existing law, we can only expect that enforcement problems will be made worse under S. 722. The bill proposes to repeal one of the most easily understood and enforceable concepts --zero level of a carcinogen-- in exchange for an ill-defined "negligible risk" standard, based on any number of risk assessment models and disagreements over their interpretation. Given this context, it will be exceedingly difficult for the public to obtain judicial review of the safety standard in the bill. The courts, on matters of "scientific" judgement, will as a rule defer to the agency's judgement. Despite EPA's past performance, the wide disagreements that exist on critical risk and data review issues, the public will be unable to challenge EPA.

V. Other Issues Are Left Ill-Defined or With Significant Room for Interpretation.

Aside from the basic underlying problems with S. 722, we find problems that could undermine its implementation, even if one could accept the underlying problems. For example:

- **Sec. 4, 408(a)(3) Processed Food.** The language suggests that for a pesticide that has a tolerance on a raw food but not on a processed version of that food (apples to apple sauce), the same residue can be considered safe if it does not concentrate above the level in the raw food. This undercuts all the specificity of risk assessment calculations implied by previous sections because it ignores the exposure component. For instance, we know toddlers drink more apple juice and eat more apple sauce than they eat apples. Therefore, the residue on raw commodities may be too high for processed versions of the same food.

- **Sec. 4, 408(b)(2)(B) Criteria for Negligible Risk.** Central to the bill is this new phrase: "not likely to have any adverse human health effect below an identifiable level, the level at which the pesticide chemical residue will not cause or contribute to any known or anticipated adverse effects on human health" and "is not likely to cause or contribute to any additional adverse human health effects in the population exposed to the pesticide chemical residue." Interesting, but this will be impossible to enforce.

- **Sec. 4, 408(c)(2)(A)(i) Risk Standard, Establishment.** This allows exemptions from tolerance where "no risk to human health" is shown. This can become very messy because it can be based on assumptions that may simply not be true. Exemptions from tolerances should not be allowed except when a chemical is not found to induce an adverse effect in laboratory animals. Also, as we have learned in the past, where a terrible chemical, like ethylene dibromide (EDB), has been exempted from tolerances and when it was later found that EPA's volatilization and thus human exposure assumptions were simply flat wrong, they had no easy, quick way to enforce against contaminated food. If it is assumed that the chemical will not appear in the food commodity, then the tolerance should be set at zero.

- **Sec. 4, 408(e)(5) Definition.** The Administration find an imminent hazard exists if the pesticide chemical residue is "significantly greater than the negligible standard." The lack of a mandatory duty and the use of the words "significantly greater" make this unenforceable.

- **Sec. 4, 408(g) Confidentiality of Data.** This provision establishes data confidentiality. It does so in such a way as to inhibit public discussion and debate. Health and safety testing data should not be confidential. Especially, companies should not be allowed to make public "data summaries" and while preventing meaningful public examination of the basis for their interpretations.

- **Sec. 4, 408(h)(3)(B)(ii) Restrictions.** Language that prohibits, "Use of data for any purpose in any court or agency of the U.S. or any state or political subdivision thereof before the decision of the Administrator on the petition for which such data were submitted. . ," would preempt a state from acting more promptly than EPA. This prohibition should be deleted to enable states to protect its residents where the federal government has failed.

- **Sec. 5(b)(4)(C) Special Risk Standard** and b(4)(D) **Negligible Risk Standard.** This requires the Administrator "to modify one or more existing tolerances" if the registrant has not met its requirements. This shifts the burden of registrant misconduct to the agency when a failure to comply with a requirement under the law should result in revocation of the tolerance. This duty "to modify" appears elsewhere and should be replaced with language that triggers a revocation of the tolerance. If it becomes EPA responsibility to engage in activities that modify tolerances for numerous uses and combinations of uses, as opposed to ruling on industry petitions for tolerances on those uses, it will force a tremendous outlay of EPA resources and time. In addition, the situation digs EPA further into the business of registering pesticides while the agency should be spending its limited time and resources restricting their use.

- **Sec. 6. Revised Negligible Risk Standard.** The bill ultimately proposes a comprehensive calculation of the risk from eating a particular commodity with residues of multiple pesticides, but fails to consider the risk from eating multiple commodities, which together present a higher risk. The bill, in effect, fails to calculate the risk from a "plate of food." This means that while an individual commodity may not pose more than a "negligible risk," exposure to numerous commodities with pesticide residues can increase the toxic body burden substantially.

VI. S. 722 Will Not Assist in Public Understanding as Risk Issues Become Clouded and Trade Groups and States Mislead the Public

NCAMP's premise: **Where a system of governmental agencies and trade associations working together are permitted on a daily basis to mislead the public on questions of pesticide risks, uncertainties and unknowns, the public expects that Congress will intervene to protect the citizens' right to know and be fully informed. "Negligible risk" will be used to distort the truth about pesticide risks and unknown hazards, in a way that misinterprets the actual facts and further clouds public understanding of the situation.**

In the midst of public concern, trade groups and some states have done more to confuse than inform the public. The thrust of the public relations brochures that are currently being distributed are intended to defuse public concern through misrepresentation of the facts. What GAO said with regard to non-agricultural pesticides in 1986, could also be said of pesticide residues on food, "The public receives misleading information on pesticide hazards."[16] For example, a recent brochure, entitled *A Consumer Guide to Food Quality and Safe Handling: Produce and Pesticides,* released by the Food Marketing Institute in cooperation with the Food and Drug Administration and distributed through food stores, makes the following incorrect statement.

> The Environmental Protection Agency (EPA) regulates the manufacturing, labeling and use of all pesticides. Before a pesticide is approved for use, the EPA requires extensive testing and safety studies to demonstrate that the product works as intended and won't pose unreasonable risks to people

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[16] GAO, *Nonagricultural Pesticides: Risks and Regulation,* Washington, D.C., GAO/RCED-86-97, 1986.

or the environment.[17]

The state of California recently published a brochure, *Food Safety (It's Hard to Know What to Believe): Here Are The Facts*, which boasts numerous untruths, such as:

> [Pesticides] are carefully evaluated by CDFA staff scientists for any human health and environmental effects. Materials which cannot be used safely are not registered. This is in addition to the review done by the federal government.[18]

These statements illustrate a severe misrepresentation of pesticide safety, in light of the incomplete testing on pesticides and outdated tolerances, but indicates more broadly how risk issues are distorted by industry and government. EPA has actually said that it does not "approve" pesticides, but simply "registers" them. We can only expect that under a "negligible risk" standard we will see further distortions of the truth and the public will be misinformed about the risk that they really face in light of the uncertainties and unknowns. S. 722 does nothing to require that clear, truthful risk information be communicated to the consumer who is to ingest carcinogens under the bill.

VII. Action Is Long Overdue

NCAMP's Premise: **Improvements can and should be made to our country's food safety laws without sacrificing our country's no additional cancer goal, as embodied in the Delaney Clause.**

NCAMP's view is that we either fix the law, so as to provide for truly protective standards for hazardous pesticides, or we continue to seek enforcement of existing law and continue to bring consumer concerns and demands directly to the marketplace. EPA's failure to enforce one law does not provide much assurance that Congress will achieve greater compliance with a new law. And if Congress intends to rewrite laws to conform to EPA's poor performance, the public will not be served.

The public's concern is well-founded. In recent years, the public has experienced numerous fiascos which support the high level of public outrage. From the ethylene dibromide (EDB) contamination of the grain-based food supply in 1983; to the heptachlor in milk and chicken stories in 1986-89, to the recent Alar™ coverage, the public has come to distrust government's ability to protect them. The challenge is to craft laws that respond to the problems, rather than cover them up.

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[17] Food Marketing Institute in cooperation with the Food and Drug Administration, *A Consumer Guide to Food Quality and Safe Handling: Produce and Pesticides*, Washington, D.C., undated.

[18] Pest Management Division, California Department of Food and Agriculture, *Food Safety (It's Hard To Know What To Believe): Here Are the Facts*, Sacramento, CA, undated.

People have told us that they do not want to eat, nor do they want their children to eat, carcinogenic pesticides. The standard of protection provided for in the bill does not meet this well-articulated consumer concern.

If one is able to accept the underlying problems with "negligible risk" and the inability to seek effective judicial review over its use –which we obviously are not, then one could find some good provisions in S. 722. For instance, the bill does incorporate inerts and metabolites into the definition of pesticide, defines drinking water as food, and appears to offer a more comprehensive look than is the case currently at cumulate risk from exposure to a number of pesticides on one commodity.

We believe that these improvements and more can and should be made without sacrificing the "Delaney Clause" and its potential enforcement. People do not want to eat carcinogens or other pesticides which can cause adverse effects. Attempting to define legal levels of carcinogens in food with existing constraints, as has been attempted in S. 722, will not protect the public but will lead to the incorporation of the unprotective "negligible risk" standard in legislation affecting a wide range of non-food exposure, causing further deterioration of our nation's health and environment.

NCAP
NORTHWEST COALITION for
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PREPARED STATEMENT OF THE NORTHWEST COALITION FOR ALTERNATIVES TO PESTICIDES

The Northwest Coalition for Alternatives to Pesticides (NCAP), a five-state coalition of citizen groups and individuals working for pesticide reform, wishes to enter the following statement in firm opposition to the proposed "Food Safety Amendments of 1989" (H.R. 1725/S. 722). We are unable to attend the hearing today because of the expense of traveling from the west coast, but appreciate the opportunity to enter the following statement into the hearing record:

Pesticide Risk Assessment Cannot Indicate Safety

While data are sometimes able to indicate that a particular pesticide's food residues (e.g., daminozide, captafol, chlorothalonil) pose high risks of cancer (or other damage), it is not possible to indicate lack of risk, given the existing data base of most pesticides.

Any of the following will contribute to an underestimation of the cancer or other risk posed by presence of a particular pesticide on food:

a. Lack of consideration and/or knowledge of the effects of (Non-)"inert" ingredients in a pesticide formulation.

b. Sensitivity of certain individuals in our genetically diverse population.

c. Particular susceptibility of children to a carcinogen.

d. Unusually large use of particular food items by individuals or groups in the society.

e. Inadequate oncogenicity testing.

f. Use of an inappropriate model for extrapolating from high doses in non-humans to low doses in humans.

g. Unforeseen combinations of cancer promoters and cancer initiators in a person's environment (food, water, workplace, school site, air contamination).

These types of factors render meaningless some EPA "determination" of the negligibility of the risk posed by purposefully adding a synthetic carcinogen to food.

H.R. 1725 Asks the Wrong Question

H.R. 1725 would commit major agency and societal resources to data-gathering, number-crunching, and cancer model debates over how much of what carcinogenic pesticide will cause how much cancer because of presence in what foods eaten in what volumes by which sectors of the society.

The citizenry is not well-served by helplessly watching risk modelers, chemical company toxicologists, representatives of environmental organizations, and overworked EPA employees battle away over how much cancer will be caused by which inadequately tested pesticides in which foods.

H.R. 1725 merely asks "How many carcinogens shall we allow to be added to our food?"

The question Rep. Waxman, Sen. Kennedy, and their Congressional colleagues should be addressing is "How do we move away from reliance on carcinogenic, teratogenic, neurotoxic, mutagenic, reproductive and chronic toxins as a way of growing food?"

Inerts and Metabolites Remain Insurmountable Problems

Although H.R. 1725 purports to address metabolites and inerts, there is no way to address them without a full toxicological data base on them and there will be no full toxicological data base on them in the forseeable future. H.R. 1725 provides for no enforceable, comprehensible guidelines regarding the identification and testing of all metabolites and inerts. The identification of metabolites of pesticide residues is difficult and complex and toxicological testing of metabolites and inerts will not occur.

What Are the Alternatives?

1. Pesticide labeling of food. Citizens will be better served if they are merely provided with information as to which pesticides may be present as residues on each food item they are buying (i.e., any possible residues from pretreatment of soil or seeds, application during growth, and/or treatment during storage or transportation). If pesticides are labeled as ingredients of food items (including the words "plus unidentified chemicals" to include unidentified inerts), the marketplace will move unacceptable chemicals out of the food production cycle far more efficiently than risk assessments based on inevitably inadequate data.

Is there any reasonable basis for denying citizens the right to know what synthetic chemicals have been added to their food?

2. Fees on sale of food use pesticides that will fund research for reduction of agricultural pesticide use. If the United States wants to move away from reliance on pesticides for growing food, then the society must provide for research, demonstration projects, and public education regarding feasible alternatives. Sweden heavily taxes (up to 25%) the sale of pesticides and uses the money for research into alternatives to pesticides. That is a society that will find ways to grow food without adding carcinogenic pesticides. How will United States farmers learn to grow their food without pesticides? By reading Swedish journal articles?

3. Citizen suit provisions for the Delaney Clause with provisions for recovery of court costs. Citizens will be willing to enforce the Delaney clause if the government does not have the time, will, or resources.

Provisions for likely enforcement of the Delaney Clause should be enacted. Whether or not enforcement provisions are enacted, the public should be informed of what pesticides (and therefore what carcinogens) may be present in the food items they buy.

Regarding Preemption of State Regulation

Finally, any attempts to limit the ability of individual states to protect their citizens from levels of pesticides judged "acceptable" by federal bureacuracies but judged unacceptable in

Conclusion

H.R. 1725/S. 722 must be scrapped rather than improved.

It is not appropriate for members of Congress to (a) decide what risks are "negligible" and "acceptable" for their constituents; (b) subject their constituents to endless wrangling by government, industry, and environmentalists about shaky numbers; and then (c) deny those citizens the right to avoid those risks by denying them access to information regarding what foods contain what pesticides.

Right-to-know will be far more powerful than inability-to-avoid-"negligible"-risk-residues at reducing risks to the public from carcinogenic food residues within a free market.

Author: Mary H. O'Brien, Ph.D. (Botany), is staff scientist with the Northwest Coalition for Alternatives to Pesticides and editor of the Journal of Pesticide Reform.

PREPARED STATEMENT OF THE U.S. PUBLIC INTEREST RESEARCH GROUP

Mr. Chairman and distinguished members of the Committee, thank you for the opportunity to submit testify on the critical issue of health threats posed by pesticides in food. The U.S. Public Interest Research Group (U.S. PIRG) is a national research and advocacy organization that serves as the national lobbying office for state PIRGs across the country. Together PIRGs have more than one million members nationwide.

Mr. Chairman you are to be commended for beginning a process that will force a formal scrutiny and hopefully a reform of the federal government's pesticide policies, especially as they relate to protecting the nation's food supply. However, before delving into this highly technical and complex issue we should remember that the overriding debate on this issue is not about science but rather social values. And Congress is an appropriate forum for such a debate. You are also to be complemented for helping shape this debate by proposing a risk only alternative to the risk-benefit authority requested by the Environmental Protection Agency (EPA).

Because those who reap the benefits of pesticides are not necessarily those who assume the risks, freedom of choice becomes an important element in this debate. This year during the Alar (daminozide) controversy, consumers turned a cold shoulder to apples and other apple products. But that was not an isolated incident. There has been a growing distrust of our food supply and the regulatory system that is supposed to protect it. A poll conducted by the Food Marketing Institute in 1987 found that 76 percent of the public believed pesticide residues in food were a serious hazard. In a democracy people should have a choice. In this case the right choice by Congress can be more protection for a growing majority of the public who are demanding safe food.

THE PROBLEM

Those least able to choose are infants and small children who are involuntarily and disproportionately exposed to much higher risks from pesticides, relative to their body weight and food consumption patterns, than adults. In an infant's first year of life his or her meals may legally contain hundreds of different pesticides, many of which are carcinogens. Even if children breast feed, studies done for the EPA have shown that most children will be exposed to several toxic chemicals in mother's milk, including the persistent DDT metabolite known as DDE -- 17 years after DDT was banned for most uses! The children of farmers and farmworkers face additional food and non-food exposures (and risks) to pesticides in their air and water. Other children will be exposed to pesticides in their yards, child-care centers and parks.

Americans have at least a one in four chance of contracting cancer and a one in five chance of dying from cancer, according to the Department of Health and Human Services (DHHS). The American Cancer Society estimates that one million new cases of cancer will be diagnosed this year. Yet we endure additional cancer risks from pesticides that begin with an infant's first meal. There should be zero tolerance of policies that risk additional cancers given the largely environmentally induced epidemic we are already experiencing. -- According to a DHHS report, "most scientists now consider that about one third to two thirds of all cancers are associated with the environment in which we live and work."

Virtually every American's daily diet may contain some of the 300 or more pesticides used on food or found in water. It is just as frightening that our laws and government allow for such a menu of poison. Even the EPA admits that many of the older pesticides, still widely used, would not be allowed to enter the market if they were developed today. However, they remain on the market through loopholes in public health protection statutes created for them by Congress and over-used by the agencies. The result is a tripling of pesticide use since 1964 (now 1.6 billion pounds a year on food). And almost nothing is done to promote alternatives to pesticides. This year the President requested zero dollars for the U.S. Department of Agriculture's (USDA) only Low Input Sustainable Agriculture (LISA) program after spending only $8.3 million on 49 of 130 eligible projects since FY 1988. Senator Patrick Leahy (D-VT) has called for $15 million in funding in FY 1990 to promote LISA's alternatives to pesticides.

While considerable attention has recently been paid to pesticides in food by the media, the focus has mainly been on Alar and its metabolite unsymmetrical dimethylhydrazine (UDMH) in apples. However, the problem is much broader than one carcinogen on one crop. In EPA's October 1988 policy statement on pesticides in food, the Agency said "there is at least 'limited evidence' of carcinogenicity (virtually all from animal studies) for 66 or more of the approximately 360 food-use pesticides already approved for use...EPA expects this number to become somewhat larger as it receives and evaluates more studies on the food-use pesticides." A study by U.S. PIRG this April (see attached findings pp. 11) found that at least 60 of these cancer causing pesticides are allowed on commonly eaten foods. Our study reported that many of these foods, such as apples, beef, corn, tomatoes, peaches and milk, may legally contain 20 or more of these pesticides. Only 11 of these 60 pesticides are even in EPA's Special Review process. The Agency seems determined to allow the use of these pesticides based on misleading or incomplete information from food and chemical companies.

In February of 1987, the EPA ranked pesticide exposures in food as its third most serious environmental health threat -- estimating a risk of 6,000 additional cancers per year. In May of 1987, the National Academy of Sciences (NAS) released a report analyzing the increased cancer risks posed by the use of pesticides on food. The NAS reported that, by volume, 90 percent of all fungicides, 60 percent of all herbicides and 30 percent of all insecticides may cause cancer. The report also reiterated that the EPA had only invoked the Food Drug and Cosmetic Act's (FDCA) Delaney Clause three times to prohibit a pesticide from being used on a food commodity, (fosetyl al on hops, amitraz and permethrin on apples).

Many of the more hazardous pesticides are used on a wide variety of crops. For example, approximately one third of all vegetables and fruits, including apples, grown in the U.S. are treated with a group of carcinogenic fungicides known as ethylene bisdithiocarbamates (EBDCs). -- (EBDCs are about 35 times more widely used than Alar.) EBDC fungicides include mancozeb, maneb, metiram and zineb. Through food processing, cooking, storage and digestion, EBDCs break down and concentrate into a carcinogenic metabolite known as ethylenethiourea (ETU). The EPA says that the "entire U.S. population is potentially subject to dietary exposure to ETU." After over 11 years in EPA's Special Review process, the Agency is expected to announce a decision to curtail some food uses of EBDCs but, predictably will not immediately suspend all uses.

EPA REFUSES TO BAN DANGEROUS PESTICIDES

All too often, the EPA gerrymanders its decisions about such matters by claiming (with no credibility) to have accurate dietary or pesticide use information that "reduces" the risks posed by a chemical. After nine years in Special Review, the EPA this year finally acted on captan. They banned its use on some foods but continued it on high volume foods such as grapes because of its "$1.2 million a year benefits" to the grape and wine industries.

The agencies need to interpret the laws correctly or ask for the enactment of stronger laws. Currently, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the FDCA are regarded within the regulated community as "industry friendly" statutes. Pesticides are automatically assumed to have benefits which the EPA usually interprets to out-weigh health risks.

In the recent case of Alar, Dr. John Moore at the EPA has repeatedly said that FIFRA and the FDCA do not allow him to quickly remove pesticides from the market. This is not true. By opting to "cancel" rather than "suspend" Alar, the EPA will allow its use for another 18 months, while cancellation procedures against Uniroyal continue. The EPA chose this route even though they agreed that Alar and UDMH residues on apples represented unreasonable risks, which exceed one cancer in a million, the Agency chose not to consider this to be an "imminent hazard." (The EPA estimates that Alar use put 9 children in a million at risk over the next 18 months.) However, the EPA has the authority under FIFRA's to suspend Alar if it makes the value judgement that 9 children in a million represents an "imminent hazard." Instead, Uniroyal finally agreed to halt Alar sales as of June 2, 1989. Meanwhile, uses of Alar can legally continue in the U.S. and Uniroyal will continue to export the chemical overseas.

EPA's insistence on balancing health risks against unproven economic benefits further clouds any effort to assess risks. Because Alar's "benefits" are largely cosmetic, the moral unacceptability of risk-benefit analysis is even more hideous. However, because Alar's metabolite UDMH may be present in elevated levels in processed food, the EPA could also have invoked the risk only provision of the Delaney Clause in FDCA which gives the Agency authority to revoke or disallow a food tolerance for a carcinogen whose residues concentrate in processed food.

The 1987 NAS report summarized some other exceptions that the EPA has made to the risk only Delaney Clause. For example, the insecticide permethrin is an oncogen which concentrates 230-fold in processed tomatoes. Instead of revoking its tolerance on all tomatoes in 1982, the EPA restricted its tomato uses to "Tomatoes Grown in Florida for Final Marketing as Fresh Tomatoes." Since then the Agency was informed that a Florida cannery was processing permethrin treated tomatoes for paste and puree.

Although Congress reauthorized FIFRA last year, the new law was accurately dubbed "FIFRA Light" in the media because it was so weak. The main improvements made in FIFRA include a 10 year time table to complete the retesting of approximately 600 active pesticide ingredients and the partial repeal of the indemnification and disposal obligations previously borne by the federal government. With the exception of the testing time table, the new law will not address many of the problems posed by pesticides today. For example, even the new retesting requirements fail to mandate comprehensive health testing for neurotoxic effects.

One excuse the EPA and FDA have is a lack of resources, but this pertains more to their work load and pace than the wisdom of their decisions. EPA's task of setting food safety limits (tolerances) on more than 8,000 food items for 300 to 400 active ingredients in over 40,000 pesticide formulas is formidable. Similarly, allocations at the FDA to carry out its responsibility for monitoring and enforcement are as bad or worse. The combined pesticide program budgets ($40 million at EPA and $14 million at FDA) total less than two hours of spending at the Pentagon. Certainly additional fees similar to the registration fees added to FIFRA last year will enhance the monitoring that the FDA and the USDA need to improve upon.

Recently some local food chains led by Raley's of California, have taken the initiative away from the EPA and FDA and have begun testing their food at private labs. -- In some cases these labs are doing a better job than the FDA. While this practice can be abused by unscrupulous retailers, those in the industry who are sincerely competing to sell certified organic foods or foods with fewer pesticide residues are at least headed in the right direction. The next step that the food industry can take is to establish more organic food sections in their produce departments. Growth in this area could be one of the best ways American farmers could compete with foreign imports.

FLAWS IN OUR CURRENT POLICIES

It is irresponsible to prescribe the continued use of these poisons, especially for use on food, when so many factors are not fully taken into account by the EPA and FDA as they "regulate" pesticides. The following are some of the well documented flaws in our current national pesticide policy that Congress needs to address:

*** The EPA fails to govern its regulation of pesticides to adequately protect the higher risks borne by the most exposed and sensitive subpopulations such as infants, children and pregnant women. Rather than calculate risks based on the proportionately higher exposures to infants, the EPA averages exposures over a life time for the entire population. This is the equivalent of saying that the river is safe to walk across because the average depth is only four feet.

*** The EPA also uses out-dated dietary data for different populations even when estimating pesticide exposure. The Agency still uses food consumption information collected in the 1960s which assumes that average adults consume no more than 7.5 ounces per year of melon, eggplant, avocados and other foods. According to the USDA children eat six times more apples than the EPA assumes. This illustrates the absolute absurdity of EPA's risk assessments because millions of Americans today eat far larger amounts of these foods. The EPA's most recent dietary data base used in its Tolerance Assessment System (TAS) is more than ten years old.

*** An October 1986 report (RCED-87-7) by the General Accounting Office (GAO) revealed that the FDA is not adequately monitoring pesticides residues in food. The GAO found that the FDA's multi-residue monitoring cannot detect 60 percent of the most hazardous pesticides likely to appear on food. Some of these include Alar, EBDCs, and their metabolites UDMH & ETU, for which the FDA tested only 125 and 76 separate samples respectively between 1979 and 1985. The FDA's tests also do not detect alachlor, the most widely used herbicide in the U.S.

*** The GAO also found that the FDA was monitoring less than one percent of domestic food and only slightly more of imported food. Even when the FDA found violations, it failed to invoke sanctions against violators or seize food before it was consumed. The GAO found that the FDA also lacked resources to do an adequate job of monitoring. For example, the FDA only allocated $13.7 million for monitoring pesticides on all domestic and imported food in 1985.

*** Another study by the GAO released on May 3 of this year reported that the EPA program to monitor the export of banned or unregistered pesticides, estimated at about 100 million pounds a year is nonexistent. "EPA received notices on only about 26 percent of the exported products" according to the GAO. This means that the countries from whom we receive as much as 25 percent of our fresh fruit and vegetables may not be getting proper warning and use information about the hazards of these banned and unregistered pesticides.

*** Only 9 states require comprehensive data on the use of an estimated 1.6 billion pounds of pesticides on crops each year in the U.S. The states are: California, Connecticut, Kansas, Maine, Massachusetts, New Hampshire, New Jersey, New York and Texas. If the FDA had better information on pesticide use in the other 41 states, it would cut monitoring costs and help improve consumption estimates.

*** While approximately 400 out of 600 pesticide active ingredients are allowed on food, only 195 have been issued new "registration standards" by the EPA (and only one of these has been fully retested for food use). EPA officials have also hinted that they may not meet the new FIFRA reregistration time tables.

*** None of the 1,200 so-called inert ingredients used on any of 40,000 pesticide formulations are required by statute to be tested or regulated based on their health effects. The EPA began requesting some test data on 110 inerts in 1987 but the Agency does not consider the added risks posed by these companion chemicals when regulating an active ingredient in food. Many, such as asbestos fibers, benzene, chloroform, formaldehyde and methylene chloride are known carcinogens.

*** The EPA also fails to calculate the added risk of exposure to other pesticide active ingredients that are likely to be on the same foods. For example, Alar is weighed by the EPA separately from the Agency's regulation of captan which is also used on apples. -- While the EPA considered other fungicidal risks and alternatives to captan it did not consider risks posed by other pesticides allowed on the same food such as Alar (a cosmetic growth regulator) or lead arsenate (an insecticide).

In this regard the Agency also fails to calculate or require data on the cumulative or synergistic effects of exposure to multiple food-use pesticides found on the same foods. This is now done, to some extent, with pharmaceutical products but is not yet part of the EPA's current risk assessments. A well known example of synergistic health effects is the several fold risk of lung cancer to cigarette smokers who are also exposed to asbestos. The level of risk is far greater than the combined risks of smoking and inhaling asbestos fibers.

*** Multiple exposures to pesticides through foods, drinking water and non-dietary exposures through the air (toxic fog) are not currently factored into the EPA's regulation of pesticides. An October 1987 USDA study reported that the ground water supply of 50 million rural Americans is at risk of contamination from pesticides used in agriculture. The EPA reported in December of 1988 that 77 pesticides have been found in the well water of 39 states. The EPA has so far proposed only 23 pesticide active ingredients for regulation under the Safe Drinking Water Act. And little regulation has been implemented to protect an estimated 300,000 farmworkers who are made ill each year from pesticides.

*** Most pesticide food tolerances were set in the 50s and 60s and reflect a "margin of safety" that errs on the side of the food grower not the consumer. Too often these tolerances were set high enough to insure that no one was caught violating them, instead of low enough to insure food safety. To now say that actual residues are usually below these tolerances is comparable to saying that few people are violating a 150 mile per hour speed limit. A March CRS report said "Current detection technology can routinely indicate residues in the parts per trillion...Most of the tolerances for these pesticides were presumably first granted when the state of the art detection method could only identify the pesticide in the part per million range."

*** The EPA is only sporadically requiring testing on neurotoxic health effects of pesticides, usually only testing for acute paralytic effects. They especially fail to require chronic neurotoxic health effects data.

*** Some pesticides such as heptachlor, toxaphene and silvex are no longer legally used on food but their residues are still indefinitely allowed to persist until they work their way out of the food chain. However, because a pesticide is no longer legally used on food does not mean that illegal use is also not a problem. There have been several well publicized incidents of illegal use of pesticides. In March of this year heptachlor tainted feed forced the destruction of four hundred thousand chickens in Arkansas and in 1985 aldicarb was found to have been illegally used on watermelons and cucumbers in California and the northwest. Only now is the Agency moving to further restrict the sale of heptachlor.

SUGGESTIONS FOR THE CONGRESS

Although S. 722 addresses a number of the issues raised above, including the elimination of explicit benefits considerations from risk assessment calculations, it does embrace the concept of negligible risk without having required a full calculation of all the uncertainties surrounding risk assessment. As risk assessment will remain an inexact science for some time to come, experience tells us that the agencies, EPA in particular, tend to abuse their discretion and provide the minimum amount of public health protection mandated under law. In this case they will almost certainly interpret negligible risk, to in effect mean "acceptable" risk, establishing a level up to which a carcinogen can be allowed on food. -- Any preventable risk of chronic adverse health effects such as cancer should not be deemed a "negligible" risk.

The EPA's abuse of such a provision is predictable because of their long-standing philosophical differences with Congress, rather than an inability to read the statute. Any agency that can illegally interpret the Delaney Clause to allow for a negligible risk, risk-benefit driven policy can easily misinterpret a risk only, negligible risk standard of no greater than 1 x 10 -6, or no more than one cancer in a million people exposed over a life time. The EPA would prefer to balance risks against benefits but if they cannot do that, they may try to balance risks against risks to avoid removing chemicals from the market. -- The recent captan decision, which considered the higher risk of alternative fungicides such as EBDCs, is an example of how they they might circumvent compliance with S. 722. Then the debate would be over whether the EPA's one in a million cancer risk was accurate. Unfortunately the courts have too often deferred to the Agency on these so-called "science" issues instead of asking whether there was a non-chemical pest control alternative available.

The irony is that many of the laudable goals in S. 722 could be accomplished by the EPA with existing statutory authority if they chose to interpret the laws correctly. And if implemented properly, current law could be used to eliminate many risks now being endured. U.S. PIRG is uncomfortable with the trade off of S. 722 for the Delaney Clause, because carcinogenic pesticides are not necessarily barred from food uses by S. 722. However, we would actively oppose legislation that contained a risk-benefit standard.

The balancing of risks and benefits is one of the main reasons the EPA has failed to effectively regulate pesticides in food. It can easily be argued that S. 722 already implies a benefit for pesticides that pose a risk of less than one in a million. And in Section 408 (b) (2) (D) (i) the bill comes close to making benefits explicit saying that a "residue shall not be established or left in effect at a level higher than the Administrator finds to be reasonably required to allow the accomplishment of the physical or other technical effect for which the use of the pesticide chemical involved is intended."

The negligible risk standard in S. 722 could also be improved in several ways that would avoid abuses of its discretionary authorities and encompass a fuller calculation of the risks posed by pesticide exposure. For example, EPA and registrants could be required to calculate exposure from a "whole plate" of food as well as the full non-dietary exposure to pesticides found in the environment. In addition, S. 722 should require the EPA to govern its regulation of pesticides by the risks posed to the 90th percentile of the most sensitive exposed populations such as infants and children. S. 722 only requires the EPA to "consider" exposure and risk to these groups.

A faster and less expensive way to accomplish this would be to phase-out all pesticides that cause cancer or tumors in animals over a period of years. A phase-out would allow time for economic adjustment by agricultural and chemical sector parties without the specter of sudden and unpredictable regulatory restrictions. -- A bill that would do this was recently introduced in the California State Assembly (AB 417).

Other improvements that should be made in S. 722 include:

--- more definitive requirements about the volume, scope and frequency of pesticide residue monitoring on domestic and imported foods.

--- higher fees levied on registrants of pesticides that have not provided practical monitoring methods so that the additional cost of single residue monitoring can be financed while methods are developed by these registrants.

--- labeling of foods with names of pesticides not yet detectable by multi-residue methods and consumer labeling of foods with the names of cancelled pesticides whose residues are allowed to persist on food.

--- strike the provision in Section 408 (b) (2) (C) that allows the Administrator to calculate exposure based on the percent of crops treated unless certified accurate records are kept on pesticides used in that state.

--- require regular (every 5 years) updates of dietary consumption patterns (EPA's TAS data base is over 10 year old).

--- specifically require test data for other chronic health effects such as neurotoxic effects.

On the positive side, S. 722 would almost certainly drive down the level of many pesticide food tolerances, their residues and hopefully uses within four to six years. Among the improvements S. 722 makes over current policy are:

+++ defining pesticide residues to include inerts and metabolites Section 2.

+++ requiring dietary exposure to be calculated at the tolerance level and include drinking water exposures in Section 408 (b) (2) (C).

+++ requiring that each pesticide have a practical method for monitoring in Section 408 (b) (2) (E).

+++ authorizing fees to cover the cost of the program in Section 408 (K).

+++ authorizing the Administrator to revoke tolerances to enforce submission of valuable new health and safety data and other requirements in Section 5 (b) (4).

+++ assessing the risks of multiple-pesticide residues on food crops after six year in in Section 6.

In conclusion, we also urge the Committee to oppose any effort to preempt the right of states to regulate pesticides more stringently than the federal government. All other major environmental statutes allow states to set tougher standards if they choose. -- If a strong federal statute is enacted that is protective of public health, states will have no reason to challenge it. Past state actions have been rare but needed when the federal government, as in the case of ethylene dibromide (EDB), failed to act responsibly ten years after the National Cancer Institute found in 1974 that EDB was likely to cause cancer in humans. Food industry representatives are quickly learning that the safest possible food supply is in their best interests and mediocre legislation is not. Consumer and environmental groups will oppose legislation that contains any form of preemption.

Thank you again for the opportunity to submit testimony on this critical issue.

CARCINOGENIC PESTICIDES ALLOWED ON 16 FOODS & FOUND IN WATER

Findings:

*** Sixteen commonly eaten foods surveyed are legally allowed to contain 54 varieties of cancer causing pesticides. (See Table I)

*** Seven of 16 commonly eaten foods surveyed are allowed to contain 20 or more known carcinogenic pesticides. These include:

Beef	(27)
Corn	(25)
Apples	(24)
Pork	(24)
Tomatoes	(23)
Peaches	(21)
Milk	(20)

(See Tables I & II)

*** Apples and milk can each legally contain over 90 different pesticide residues, 36 of which are carcinogenic. (See Table II and Appendix B) Many of these pesticides are still not fully tested for their health effects.

*** Some of the most well known of the 54 pesticides studied include: alachlor, captan, daminozide, dinoseb, heptachlor, EDBC's, and parathion. (See Table II)

*** At least 25 of these carcinogens are among 77 pesticides that are also found in well water. (See Table III)

*** A total of 33 carcinogenic pesticides were among those found in well water, (including 8 not allowed on food). (See Table III)

Table I

NUMBER OF CARCINOGENIC PESTICIDES ALLOWED ON 16 COMMONLY EATEN FOODS

A Hypothetical Pesticide Menu

Breakfast: Pork Sausage
Eggs
Whole wheat toast with orange marmalade
Orange Juice
Milk

Lunch: Chicken
Rice
Broccoli
Apple Juice

Dinner: Steak
Baked Potato
Corn on the cobb
Fruit cocktail with grapes and peaches

Total legally allowed cancer causing pesticides on all three meals: 54 different carcinogens. (See List below & Table II)

Disclaimer: This scenario uses a similar assumption made in the 1987 National Academy of Sciences report, "Regulating Pesticides in Food," that all crops are treated with all of the pesticides allowed on those crops. It is not likely that all of these pesticides would be used simultaneously and have all of these detectable residues as well. However, the point here is that if it did happen, it would be perfectly legal. Many other pesticides are also allowed on these foods, most of which are not fully tested. We have only listed, in table II, those pesticides which are thought to cause cancer.

Commodity	Number Of Pesticides
1. Apples	24
2. Beef	26
3. Broccoli	11
4. Corn	25
5. Eggs	18
6. Grapes	17
7. Lettuce	14
8. Milk	20
9. Oranges	17
10. Peaches	21
11. Pork	24
12. Potatoes	17
13. Poultry	17
14. Rice	7
15 Tomatoes	23
16. Wheat	16

Appendix B—Food Use Pesticides With Evidence of Carcinogenicity

Active ingredient	Group [1]	408 Tolerances food	409 Tolerances food	Needs [2] 409 tolerances
1,3-dichloropropene [4] [5]	B2			
2,4-D	D	x	x	
Acephate	C	x	x	
Acifluorfen	B2			x
Alachlor [5]	B2			x
Aliette (fosetyl al.)	C			
Amitrole	B2			
Amitraz	C			x
Arsenic acid (orthoarsenic acid)	A			
Asulam	C			
Atrazine	C			
Azinphos-methyl	D			x
Benomyl [5]	C	x		
Bifenthrin [5]	C			
Bromoxynil				
Calcium arsenate				
Captafol	B2			
Captan [6]	B2	x	x	
Chlordimeform & hydrochloride	B2			
Chlorobenzilate				
Chlorothalonil	B2			
Copper arsenate				
Cypermethrin				
Cyromazine [4]			x	
Daminozide [6]	B2	x	x	
Diallate				
Dicamba [7]		x	x	
Dichlorvos (DDVP)	B2	x		
Diclofop methyl				
Dicofol	B2	x		
Dimethipin (Harvade)	C			x
Dinoseb	C			
EDB	B2			
Ethalfluralin			x	
Ethylene oxide [5]		x		
Folpet	B2			
Gardona	C	x	x	
Glyphosate	D	x	x	
Lactofen [5]	B2			
Lead arsenate				x
Lindane	D			x
Linuron [5]	C			
Mancozeb [4] [6]	B2	x		
Magnesium arsenate				
Maneb [4] [6]	B2			x
Methanearsonic acid			x	
Methidathion	C			x
Methomyl [5]				x
Metiram [4] [6]	B2			
Metolachlor	C			
Oryzalin	C	x		
Oxadiazon	C			
O-phenylphenol				
Paraquat	E	x	x	
Parathion	C			
PCNB (pentachloronitrobenzene)	D			
Permethrin				x
Phosmet	C	x		
Pronamide	C			
Propazine	C			
Propiconazole [5]	C			
P-dichlorobenzene [5]	C			
Sodium arsenate				
Sodium arsenite				
Terbutryn	C			
Tetrachlorvinphos		x		
Thiodicarb [5]				x
Thiophanate methyl [5]				x
Toxaphene			x	
Triadimefon (Bayleton)	C			
Tridiphane	C			
Trifluralin	C	x		
Zineb [4] [6]	B2			

Notes:

[1] Classification in accordance with EPA's Cancer Assessment Guidelines (see Appendix A) for those chemicals for which a weight-of-the-evidence determination has been made.

[2] Chemical has recently been determined to require a 409 tolerance.

[3] Registered uses (formerly not considered to be food uses) which have recently been defined as food uses.

[4] Included due to potentially oncogenic metabolite.

[5] Recently added to list because of newly registered food uses.

[6] Currently in Special Review for dietary concerns.

[7] Included because a contaminant is an oncogen.

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[3] Theoretically, this assumption is based on the premise that smaller animals, which eliminate heat from the body (an indication of metabolism) more efficiently than larger animals, are more efficient metabolically at detoxifying a chemical than larger animals. This difference in heat elimination has been related to the ratio of the surface area to the volume of the organism. Mathematically, the correction for surface area differences is made by dividing the dose in the animal study by the ratio of human body weight to test animal body weight to the two-thirds power.

By Peter W. Tonge

ENVIRONMENT

The No-Pesticide Revolution

Farmers everywhere are seizing on what the Chinese knew centuries ago—that voracious spiders and other natural enemies of pests can control them more effectively, cheaply, and safely than chemical poisons.

NIGERIA: The plane banks to the left over lush forest, then dives in for a low run over an expansive field of cassava, the staple food for more than 200 million people in tropical Africa. The aerial maneuvers are much like those of any crop-sprayer in the American Midwest. But this aircraft is different. It trails no clouds of drifting spray. Instead, it disperses tiny wasps by the tens of thousands, ejecting them through a special tailpipe, like so many darts from a Pygmy blowgun.

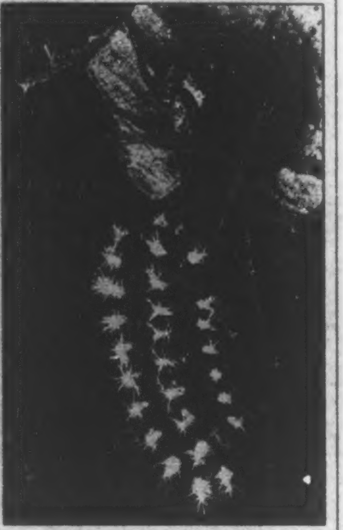
The purpose is to control the cassava mealybug that, in the decade following its accidental introduction in 1973, spread like a prairie fire from one side of tropical Africa to the other. And the program is proving highly effective. Reports of cassava fields returning to life within weeks of the plane's passing are coming in to the Institute for Tropical Agriculture in Ibadan, Nigeria. Scientists there estimate that for every $1 spent on the program, $178 is being returned in harvests saved and lives less disrupted. More important, the specter of a famine even worse than the drought-induced one in Ethiopia is waning.

INDONESIA: Half a world away in Indonesia a farmer goes out to his rice paddies and releases voracious wolf spiders. Packages of these and other natural predators indigenous to the area are provided by the government, because earlier applications of pesticides had killed most of these beneficial creatures. A United Nations Food and Agriculture Organization program has proven these insects to be more effective in controlling the brown planthopper than the chemical sprays that such farmers once used routinely.

Yields are up, costs are down throughout the rice-growing regions, and a satisfied Indonesian government has banned the sale of 57 pesticides. Now it is actively promoting this form of pest control, the first government in the world to do so.

The Indonesian farmers, however, are doing no more than their counterparts in mainland China have done for centuries—nurturing and protecting the predatory spiders. Chinese farmers, knowing the spiders' appetite for brown planthoppers, have long placed bundles of straw in their rice fields to provide safe havens for the spiders to retreat to during harvest and flooding periods.

UNITED STATES: In California's Central Valley almond growers release predatory mites into their orchards. They've been doing so for four years now with impressive results.



NATURAL PEST CONTROL: *Shield bug, a beneficial predator, attacks leaf-eating caterpillar. (All photos © Edward S. Ross)*

The Western predatory mite (*Metaseiulus occidentalis*) is a common enough creature that feasts on the tiny but destructive red spider pest. But the predatory mites being released now are a superior strain. They were selected and bred in the labora-

Peter W. Tonge, for many years a writer on gardening for The Christian Science Monitor, uses his own garden for research.

Chemicals have left many pest populations greater than they ever were.

tories of Dr. Marjorie Hoy at the University of California at Berkeley for an important quality: their resistance to several chemical pesticides. As a result, growers can now spray to control the codling moth (for which no effective biological control is currently available) without destroying the natural predators of the red spider.

For the 65% of Central Valley almond growers who have adopted the use of predatory mites, the saving in pesticide costs is estimated at some $21 million a year. The program has now been adopted by apple, pear, and grape growers in the valley as well.

Nigeria, Indonesia, California—three widely separated parts of the world, with different climates and dissimilar cultures, all with one common denominator: the increasing practice by local farmers of "integrated pest management." IPM, as the abbreviation has it, embraces biological and other nonchemical approaches to pest control, reserving the use of chemicals for rare situations in which effective alternatives are not known or not available.

Sheila Daar is executive director of the Bio-Integral Resource Center (BIRC) in Berkeley, California, a nonprofit organization specializing in "the least toxic methods" of pest control. Speaking to a gathering of Massachusetts nurserymen recently, she said of chemical pesticides: They have a place in IPM but "usually as a last resort, seldom a first resort, and never as the only resort."

In a follow-up interview Ms. Daar explained when a pesticide might be a first resort: "If the pest has already reached epidemic proportions when we are called in, we would use a spray." But that spray would be "target specific," one that only the pest was vulnerable to, or else "it would break down quickly in the environment so that within a week or two we could introduce the natural enemies that would hold the pest in check from then on."

The use of predators, parasites, and pathogens—or "beneficials," to give them their collective name—is in line with the use of pest attractants and traps and such practices as crop rotation. They add up to what is increasingly being recognized as effective pest control, vital for the environmental health of a planet becoming dangerously overchemicalized.

Writing in the IPM Practitioner, which he co-edits with Ms. Daar, William Olkowski describes the use of natural enemies as having "one of the most amazing and cost-effective records in pest control." While crop losses to insect pests have almost doubled since 1940 despite a 10-fold increase in the use of insecticides, "the biological control record tells a different story," he says. For instance, work by Dr. Ken Hagen of the University of California shows that the introduction of natural enemies has brought 60 major pests under complete biological control, 60 under substantial control, and 40 under partial control.

Long ignored by conventional agriculture, IPM has made significant strides in the past decade, not least because chemicals have failed to justify the confident forecasts once made for them. Instead of winning the pest-control war, chemicals have won a series of battles, achieving temporary control, often at long-term cost. By upsetting the natural order and destroying insects beneficial to the farmer, chemicals have left many pest populations greater than they ever were. As Ms. Daar likes to put it: "When we destroy the beneficials, we inherit their work."

As early as 350 B.C. the Chinese began introducing tailor ants (*oecophylla*) into citrus orchards to control caterpillars and boring beetles in some of the earliest known instances of managed natural pest control.

But modern-day biological pest control was born in the United States exactly 100 years ago this year when the vedalia beetle rescued the California citrus industry from the brink of disaster. The tiny orange-and-black Australian ladybug was brought in to control an outbreak of scale that defied all chemical controls known at

***ANCIENT REMEDY:* Tailor ants in Liberia and Gabon (inset) are of the family used to control orchard pests in China millennia ago.**

[illegible]: To combat cotton bollworm (left) daughters of Texas pest-control operator put cards of parasitized bollworm eggs in paper cups (center) and hang them on plants (right) in cotton fields. This system has controlled the pest in some 10,000 acres.

the time. The maneuver was so effective ("miraculous" was a common comment of the day) that the crop made it to market that year against nearly all expectations.

That promising start with natural controls faded with the development of ever more powerful chemical insecticides in the industrialized West. DDT was the "wonder" insecticide that shaped society's views, beginning in the late 1940s. But, as Sandra Postel puts it in Worldwatch Paper 79, "Defusing the Toxics Threat: Controlling Pesticides and Industrial Waste," some "ugly surprises" were to "cast dark shadows over DDT's many blessings" so that today it is banned or restricted in many countries. Initially, though, DDT was seen as "almost too good to be true," in the words of a British entomologist of the day, and it led to the somewhat cavalier belief in both industry and society as a whole that chemicals would provide *the* answer to pest control.

[illegible]: Australian ladybird (British Museum display, left) checks citrus scale. Another species (right) feeds on aphids in Thailand.

Under the circumstances, it was almost inevitable that chemicals would be overused, particularly given society's poor understanding of nature's system of checks and balances. Dr. Robert Metcalf, professor of entomology at Illinois State University in Normal, Illinois, lists some of the many consequences of this thoughtless approach.

- When cotton plantations in Sudan were sprayed to get rid of the bollworm, the natural enemies of the whitefly were eliminated. The resulting harvest was so contaminated by the sticky honeydew exuded by the fly that not one bale of the cotton could be ginned.
- In northeastern Mexico, cotton has declined to a fraction of its 1960s prespray acreage, because the tobacco budworm (a cotton pest as well) developed immunity to the sprays more readily than its natural enemies did.
- For the same reason, the bollworm became a more vigorous cotton pest in the United States. In economic terms, Dr. Metcalf says, farmers were better off before they began spraying for the pest.
- The corn rootworm was a relatively minor pest in the US until the postwar years, when first BHC, then aldrin, chlordane, and heptachlor, all soil insecticides, were thrown at it. By 1959 the rootworm had developed resistance to all these insecticides and began proliferating. Today it is the No. 1 corn root pest in the US. Although some of the newer pesticides still are effective, there is evidence that *Diabrotica virgifera*, to give it its Latin name, is becoming resistant to these, too. (By contrast, crop rotation is a simple, inexpensive, and very effective IPM approach: The pest is starved out of the soil in a year when an alternate crop is grown.)
- In Indonesia the government has embraced IPM because the principal pest of rice, the brown planthopper, has become a "superbug" by developing immunity to more than 15 pesticides.

In 1938, says Ms. Postel, scientists knew of just seven pests that had acquired resistance to chemicals; by 1986, the number had grown to 447. To this observation Ms. Dear adds that the wolf spider, or the spined soldier beetle, or any other pest predator, for that matter, doesn't much care whether the meal of its choice has developed a resistance to pesticides or not.

Finally, economic realities have begun driving the IPM train full speed ahead. For example, in south Texas cotton fields, where insecticide use has decreased 88%, farmers' average yearly return has increased an estimated $31 an acre where IPM practices have been undertaken.

Worldwatch Institute research also shows that:

The $32,250 spent by Sri Lanka to naturalize imported parasites in its coconut groves during the early '70s now prevents crop losses valued at $11.3 million annually.

Parasitic wasps are controlling stem borers at one-third the cost of chemical control in the sugar cane plantations of Guangdong Province in China.

Pesticide use dropped between 80% and 90% in the seven years after IPM was introduced in Brazilian soybean fields.

Natural enemies of banana pests reinvaded Costa Rican banana plantations after the use of chemical insecticides ceased, and they are effectively

For More Information

Worldwatch Institute, 1776 Massachusetts Avenue NW, Washington, D.C. 20036, provides a publications list on request.

Bio-Integral Resource Center, P.O. Box 7414, Berkeley, CA 94707, will supply a publications catalog at cost ($1).

controlling pests. And the list continues.

Among the more exciting natural control programs of recent years is the campaign against the cassava mealybug in Africa. The Portuguese brought the cassava plant from Brazil to Africa almost 500 years ago. It thrived in the warm tropical regions of Africa, spreading in a broad band from one coast to the other. In the developed world the cassava is known principally for the tapioca dessert that is made from it. But in Africa it is the principal source of calories for some 200 million people in 31 countries.

The cassava flourished in Africa without any major pest to threaten it until the early 1970s, when one was accidentally introduced, probably in some botanical specimens that came from South America. The small but voracious cassava mealybug, hitherto unknown to science, turned up in Zaire in 1973 and, lacking natural enemies, quickly spread across Africa, devastating cassava plantings. Harvest losses above 80% were frequent. A severe famine appeared imminent unless the mealybug could be controlled.

So, late in 1979, the Institute for Tropical Agriculture in Ibadan, under Swiss-born Dr. Hans Herren, began searching for a biological control agent. The pest was so widespread that chemical sprays could never be effectively applied and, in the quantity needed, would be both unaffordable and threatening to the environment. Natural enemies, on the other hand, would establish themselves and migrate to other regions as the pest had done in the first place. Once established, they would maintain themselves; repeat "spraying" would be unnecessary.

But first the original habitat of the hitherto unknown cassava mealybug had to be uncovered; there, scientists knew, they would find its natural enemies as well. After several years of fruitless searching, scientists found the pest almost by chance in Paraguay well away from the area they had expected. Of the 60 natural enemies found there, 15 have been brought to Africa, and one has proved exceptional: the parasitic wasp *Epidinocarsis lopezi*. The wasp lays eggs in the body of the mealybug, which perishes as the wasp larvae develop. That the parasite reproduces more rapidly than the pest increases its effectiveness dramatically. It has been found to spread 30 to 60 miles from the release sites in a single dry season.

Meanwhile, the airplane releases are continuing in the hope of "seeding" the entire cassava belt with the little wasps by the early 1990s. Scientists say it is unlikely that the wasp will ever destroy the cassava mealybug in Africa, but they expect it to keep the pest at economically acceptable levels, each species maintaining the other in a natural balance as they do in Paraguay.

Worldwide the search for new and more effective biological controls for insect pests goes on. From Berkeley's Dr. Hoy comes news of another breakthrough: the discovery of a parasitic wasp to control the walnut aphid—a wasp that can withstand codling moth insecticides. This form of immunity was previously believed to be unattainable in parasites.

The San Diego-based Mycogen corporation has just gained approval from the Environmental Protection Agency for a long-lasting bacterial insecticide that is highly effective against the Colorado potato beetle while leaving beneficials unharmed.

Meanwhile, there is encouraging news on the chemical side of the equation. According to Ms. Dear, research emphasis is moving away from the broad "kill everything in sight" kinds of pesticide toward those that target a narrow range of insects and break down rapidly in the environment.

Other IPM breakthroughs can be expected as research continues. But the most important one of all has come about slowly over recent years, according to Dr. Metcalf. It is "the growing realization that the other [all chemical] road is the road to ruin."

[illegible]: A syrphid fly (above, top) lays eggs among aphids; larva (above, bottom) has a ready food supply of aphids, which damage plants by sucking their juices. Parasitic wasps (top right) emerge from chrysalis of a much larger insect.

PREPARED STATEMENT OF THE PUBLIC CITIZEN LITIGATION GROUP

Public Citizen[1] appreciates the opportunity to submit this statement on S. 722, the Food Safety Amendments of 1989. Public Citizen has a longstanding interest in promoting and enforcing laws designed to assure the safety of the nation's food supply. In past years, Public Citizen's Litigation Group has brought cases seeking a ban on Alar, more stringent regulation of aflatoxin, and a ban on cancer-causing color additives.

As the Committee is aware, pesticides are regulated under two different laws -- the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FDC Act). FIFRA applies to all uses of pesticides, whereas the FDC Act applies only to uses of pesticides on foods. As is appropriate, the standards in the FDC Act are more stringent than the more general standards contained in FIFRA. For example, whereas FIFRA appears to require a risk-benefit balancing, such a balancing is not required by the Food, Drug and Cosmetic Act. In addition, Congress adopted a particularly stringent regulatory approach for pesticide residues in processed foods.

We believe that pesticides are the most dangerous category of preventable substances that are currently found in the food supply. When the Food and Drug Administration finds evidence of carcinogenicity of a single food additive, a public controversy immediately arises. This is the basis on which the FDA proposed to ban saccharin, as well as Red Dye No. 2 and a number of other food and color additives. (The saccharin ban was later overturned by special congressional legislation.) But the list of pesticides for which there is animal evidence of carcinogenicity have become commonplace and accepted. As recently as October 1988, EPA identified 66 pesticides for which it has evidence of carcinogenicity. EPA has seriously failed to provide strong regulation that gives the public the assurance of safety to which it is entitled.

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[1] Public Citizen is a nonprofit consumer and environmental organization founded by Ralph Nader in 1971. Congress Watch is the legislative advocacy arm of Public Citizen. The Litigation group is a public interest law firm that uses the courts to enforce laws that Congress has enacted.

The public's reaction to the "60 Minutes" story on Alar is extremely informative. First, it demonstrates that the public has very little confidence in EPA. It does not believe that federal regulation currently assures the safety of pesticides. Second, it demonstrates that the public cares deeply about carcinogenic pesticides and wants laws and federal regulatory agencies to ensure to the maximum extent possible that cancer-causing pesticides do not appear in the food supply.

Third, the Alar story shows that consumers and the industry both have a vital interest in strong regulation. Only through strong and effective regulation will the public's confidence be restored and will industry be saved from the devastating impact of future Alar controversies.

The true significance of the Alar story is that Alar is not unique. There are many other pesticides currently being used that have risks approaching those of Alar. These pesticides have not been adequately regulated by the Environmental Protection

Agency, and, like Alar, they could be eliminated from the food supply without any substantial loss to industry. Unless EPA begins a program of vigorously enforcing the existing law, Alar may be only the first in a series of pesticide stories that have a major impact on particular food commodities.

There are two approaches that could be taken in order to improve EPA regulation of pesticides. The first would be to use the current law to begin effective regulation of pesticides in food. The second approach would be to adopt legislation directing EPA to take such an approach. I will now address each approach.

I. The Laws Applicable to Pesticides Should Be Used To Protect The Public.

The reason that pesticides are currently regulated inadequately cannot be attributed to weaknesses or omissions in current law. Instead, the problem is EPA's inability or unwillingness to implement the current law in a manner that adequately protects the public. Today, EPA has the authority to implement most, if not all, of the measures in S. 722 that are designed to strengthen the laws applicable to pesticides. For example, EPA could interpret the safety standards in the Pesticide Amendments to the Food, Drug and Cosmetic Act, 21 U.S.C. 346(a), as requiring pesticides to meet a negligible risk standard, and it could adopt the definition contained in S. 722. The FDC Act suggests that EPA could also exclude consideration of benefits, as does the judicial decision of

Environmental Defense Fund v. HEW, 428 F.2d 1083 (D.C. Cir. 1984). Indeed, EDF v. HEW implies that the agency could adopt a rule that would prohibit any pesticides that are animal carcinogens and leave residues in food. Similarly, the agency could adopt a program to ban the pesticides associated with the most serious risks within a specified period of time, as required by S. 722. It could also adopt the approach to regulation of inert ingredients that the bill requires.

EPA has taken none of these steps. Instead, it has used its energy to weaken current law, in our view illegally. I am referring to the agency's recently-announced policy of refusing to apply the Delaney clause to pesticides currently on the market that were found to be carcinogenic after they were licensed, and of not applying the Delaney clause to new pesticides where the risk is less than one in a million (the de minimis policy).

I would like to emphasize that the Delaney clause has only a limited application to pesticides. It does not apply to pesticides on raw agricultural commodities. It applies only to pesticides in processed foods that concentrate at higher levels, levels greater than are permitted on raw agricultural commodities. 21 U.S.C. 342(a)(2)(C), 348.

Where it does apply, the Delaney clause prohibits the approval of a substance that causes cancer in animals. There is no absolute prohibition on pesticides that cause cancer in animals except where the pesticide concentrates in a processed food at levels above the tolerance permitted on raw food. Such a residue would be illegal on raw food, since it would be above the permitted tolerance, and we believe that Congress acted sensibly in prohibiting such residues on processed food as well. For example, in the case of Benomyl, EPA has set the tolerance in grapes at 10 ppm. 21 C.F.R. 180.294. Since EPA has found Benomyl to be an animal carcinogen, then the Delaney clause prohibits the agency from setting the tolerance in processed food at a level that is above 10 ppm. However, the current tolerance for Benomyl in raisins is 50 ppm, 40 C.F.R., 185.350, a clear violation of the Delaney clause, in our opinion.

In recent years, EPA has been identifying more and more pesticides that are animal carcinogens. Many of these concentrate in processed foods, and thus their use is illegal under the Delaney clause. In order to address this issue, several years ago, EPA referred the question to the National Academy of Sciences which published a book-size study on the matter. Regulatory Pesticides in Foods: The Delaney Paradox (National Academy Press 1987). The NAS recommended that the pesticide laws be strengthened, and that the Delaney clause application be removed, an approach that is very similar to the one taken in S. 722. While the report is silent on the question of whether EPA could strengthen the regulations of pesticides without Congressional action, a fair reading of the Report shows that it is quite clear that the NAS believes that legislation would be required to remove the application of the Delaney clause to pesticides in processed foods.

Subsequently, Representative Waxman introduced H.R. 4739 in the House of Representatives (June 3, 1988), and hearings were held in June 1988. Nevertheless, without waiting for legislation, in October 1988, EPA unilaterally issued a policy eliminating most applications of the Delaney clause to processed foods by declaring that the Delaney clause does not apply retrospectively and by adopting a de minimis interpretation of the Delaney clause. 53 Fed. Reg. 41104 (October 19, 1988). We sued the Food and Drug Administration when it adopted a de minimis interpretation to the Delaney clause in the Color Additive Amendments to the Food, Drug and Cosmetic Act. 21 U.S.C. 376(b)(5)(B). A unanimous panel of the United States Court of Appeals for the District of Columbia Circuit upheld our position in Public Citizen v. Young, 831 F.2d 1108 (D.C. Cir. 1987) that such a de minimis interpretation is impermissible.

A few weeks ago, Public Citizen, the Natural Resources Defense Council, the Attorney General for the State of California, and the AFL-CIO all joined in a lawsuit and petition to require EPA to implement requirements of the Delaney clause and other provisions of the pesticide laws in a manner that would improve the protection of the public health. The lawsuit would require EPA to adopt a plan to collect data on all residues of pesticides in processed foods. The petition argues that EPA is legally required to apply the full force of the Delaney clause to prohibit the use of pesticides in processed foods at levels greater than allowed in the raw products.

These efforts would be moot and would not be necessary if S.722 is adopted into law. However, should Congress decide not to act, we intend to use the courts to the fullest extent possible to pressure EPA in a constructive way to utilize provisions of federal law that are designed to protect the public from unnecessary exposure to cancer causing pesticides.

II. S. 722 Would Also Address the Public's Concerns About the Safety of Pesticides and Is a Significant Improvement Over Current Laws

Just last year, Congress adopted amendments to the Federal Insecticide, Fungicide, and Rodenticide Act. These amendments contain timetables for EPA's action on pesticides. However, the 1988 amendments to FIFRA are not sufficient to protect the public from pesticides in foods. If EPA takes all the time allowed, it will be almost 20 years before it reviews all the pesticides covered by the FIFRA timetable. In addition, the timetable does not apply to most pesticides in foods. Therefore, it is important that Congress specifically address the issue of pesticides in foods.

While we take issue with some of the provisions in S. 722, we support the bill because it significantly strengthens current law in a way that would force EPA to do a better job in regulating pesticides. The most significant weakness in the bill is its failure to include a mandatory phaseout of all pesticides found to induce cancer in animals. In this regard, the bill is weaker than current law, which bans cancer-causing pesticides in processed foods that concentrate above the tolerance in the raw product. Public Citizen supports a phaseout of all cancer-causing pesticides.

The bill contains a number of important strengths. We regard it as particularly important that Congress eliminate the consideration of benefits in evaluating pesticides. The Food, Drug and Cosmetic Act takes this approach with respect to food additives, color additives, and a number of other substances. Thus, in determining whether to allow the use of a food additive, the FDA evaluates only the risk of the substance, and will ban the food additive if it finds that it is not safe. The same approach should be adopted for pesticides.

The principal problem with permitting the consideration of benefits has already been identified in the hearings. There is no acceptable method of balancing a pesticide's monetary benefits to industry against its risks to consumers. Although the benefits provision has been in current law for 35 years, EPA has yet to design any systematic means of measuring benefits or any method of weighing those benefits against human health risks. The benefits provision makes EPA's decisions as to whether to allow pesticides on the market almost completely discretionary, insulating those decisions from any effective review by either Congress or the courts. No case has been made that pesticides have any health benefits that would justify exposing the public to significant risks.

The public wants and is entitled to assurances that the pesticides in their foods are safe. As long as a benefits provision is contained in current law, that assurance simply cannot be given.

The bill also contains a number of other important provisions that are designed to better protect the public health, including the provision requiring more stringent regulation of inert ingredients used in pesticides, the provisions requiring EPA to ban the most dangerous pesticides within four years, and the provision which attempts to provide a more precise definition of the level of risk that will be permitted in pesticides.

In summary, Public Citizen supports S. 722. We urge the Committee to amend the bill to phaseout the use of cancer-causing pesticides in foods and to issue a favorable report.

PREPARED STATEMENT OF DR. WILLIAM LIJINSKY

Mr. Chairman and members of the committee, thank you for allowing me to present my views on the problem of regulation of pesticides in the food supply, an issue of great importance in protecting the Public Health. I am William Lijinsky and am providing my personal opinions, not those of the United States Government nor those of my employer, Bionetics Research, Inc. I would like to address briefly the cautions that must be considered before changing the present condition. These are based on more than 35 years of study of chemical carcinogenesis.

Cancer is probably the most fearful disease to people in the industrialized world, afflicting 1 person in 4 and killing 1 person in 6. This is a new pattern of the 20th Century, following the reduction through hygiene and better habits of the common infectious diseases. The experimental work that began early in this century revealed that chemical compounds of certain types possessed the property of inducing cancer in animals. Succeeding studies of several thousand chemicals showed that about 10% were carcinogenic, although this proportion is not very informative, since many compounds were tested because they were believed likely to induce tumors. Among them were many pesticides and other agricultural chemicals, and several of them were carcinogens.

Within the past 20 years carcinogenesis tests have become more precise and sophisticated, instead of the hit-or-miss studies that were common before that. They were designed to provide reasonable certainty that the test substance posed little or no risk of cancer when humans were exposed to it. Dr. Umberto Saffiotti and I helped design those tests. Because of the expense of the tests, the substances chosen for testing in these systems (using many animals of two species at two dose levels) were not random. They were substances already suspect because of prior experiments, or because they resembled known carcinogens in structure, and because they had some economic importance. Fewer than half of those tested were carcinogenic, many were active only in one species (usually rats or mice) and some only in one sex. However, by definition, any substance that induced cancer in even one sex or one species was a carcinogen, and more likely to pose a cancer risk to humans than a substance that was not a carcinogen in those tests. Because of the well-documented differences between species in response to a particular carcinogen, it cannot be said with certainty that a substance that does not induce tumors in either rats or mice would not pose a carcinogenic risk to humans; it is an assumption we must make in the absence of any alternative means of testing for carcinogenic activity.

There have been many suggested short term assays for detecting potential carcinogenic activity, most of them based on the unverified assumption that induction of tumors takes place by a mutagenic mechanism. The most commonly used are assays that produce colonies of mutated bacteria, such as that introduced by B.N. Ames of the University of California, Berkeley, and they have been useful. However, in recent analyses of the results of testing in such assays compounds that had been examined in the long term bioassays carried out by the National Cancer Institute and later by the National Toxicology Program, there was little more than 50% correlation between carcinogenicity and activity in the short term assays (Tennant et al., 1987; Zeiger, 1987). Therefore, the abbreviated assays cannot be considered predictive of carcinogenic activity, and the chronic and expensive animal bioassays are all we have.

The causes of most human cancers are not known, but tobacco use is related to a considerable proportion, although we do not know which components of tobacco or tobacco smoke are responsible for tobacco related cancers. Diet has also been associated with certain patterns of cancer, but the data are imprecise and the carcinogens are unidentified. According to the epidemiologists Doll and Peto only about 4% of human cancer can be attributed to occupational or industrial exposures to carcinogens, which leaves a large gap to be occupied by "unknown causes". Among these lie environmental carcinogens, including agricultural chemicals, food additives, food constituents and possibly carcinogens formed within the body (endogenous carcinogens). There are certainly some cancers that have a direct genetic origin, perhaps defective genes, but these seem to be small in number. The slowly accumulated evidence of epidemiology shows that cancer incidence has more to do with where people live than with their genetic background, as shown in the figures of migrant populations. For example the common cancers of second generation Japanese people in Hawaii resemble those of other Americans rather than those of people in Japan. The cancer patterns of Black Americans resemble those of all Americans and differ from those of people in West Africa. This evidence from very large populations (much larger than the groups of animals on which we do our experiments) shows that exposure to carcinogenic agents is the main source of cancer in humans.

What animals experiments tell us

1. Well-conducted 2-year bioassays of substances in 2 species of rodents at high but non-toxic doses that give rise to statistically significant numbers of tumors compared with controls in at least one sex of one species identify them as carcinogens. Substances that do not give this result are assumed to be non-carcinogens.

2. Exposure of humans to substances identified as carcinogens are assumed to pose a carcinogenic risk to them. The magnitude of this risk cannot be calculated with present knowledge and estimates may be off by several orders of magnitude.

3. It is not possible to conduct plausible experiments which enable us to establish a safe threshold for exposure of people to any carcinogen revealed through experiments in animals. Few dose-response studies over a large range of doses have been carried out and in those, mainly with nitrosamines, there have been significant tumor responses even at the lowest doses used, which were lower than those to which workers in some occupations are exposed (nitrosodimethylamine, Peto et al., 1984; nitrosomorpholine, Lijinsky et al., 1988).

4. Comparing the carcinogenic effects of compounds in several species has

indicated that there is no way to predict the potency in one species from that in another. However, a substance carcinogenic in rats, for example, is more likely than not to be carcinogenic in mice, and vice-versa (Haseman and Huff et al., 1986). It is consistent with protection of the public health to assume that man is as susceptible as the most sensitive species in which the substance has induced tumors.

5. There is no basis for assuming that the response of humans or animals to a carcinogen is related to the lifespan of the species. The little information relating to this subject that we have, for example the experiments of Schmähl in rats, chickens, cats and snakes, of very different lifespan, show that the time of appearance of the tumor is roughly related to the dose administered, independent of the lifespan (Schmähl and Scherf, 1984; Schmähl et al., 1978). Therefore, cancers usually appear late in the life of humans because they are exposed to low doses of carcinogens over a long period, compared with our experimental animals.

6. Experiments in which animals are exposed to combinations of carcinogens show that the effects are usually additive, as is the case with increasing doses of a single carcinogen. Increasing doses of a carcinogen (or several) decreases the time of appearance of tumors and increases the incidence, and vice-versa. Therefore the effects of low doses of a carcinogen, such as humans might experience, when repeated and combined with the effects of other carcinogens, accumulate over time (60 years or more, in the case of people exposed as children) and increase the probability that cancer will develop.

7. The long time that elapses between exposure to carcinogens and the appearance of tumors differentiates carcinogenesis from most other kinds of toxicity. Tumor cells implanted into receptive animals grow very rapidly into tumors, in a few weeks, whereas induction of tumors by chemicals always takes months. The process of transforming normal cells into tumor cells must have many stages,none of which is understood. Even the commonly accepted beginning of the process as a mutation (or several) in DNA of the nucleus is not a fact, since several substances that are not mutagens are quite effective carcinogens.

In view of the small amount of information about the mechanisms by which chemicals give rise to cancer (and the uncertainty about the relevance of that information), it is unwise to permit officials or experts to calculate tolerable or "safe" exposures for humans to carcinogens. All of us are fallible even when armed with sound information. Reliable information about carcinogens is limited almost to whether or not the substance is one.

The argument that has been advanced, but is not accepted by most investigators in this field, that human exposure to "natural" carcinogens in plants used as food is much more important than exposure to industrially produced carcinogenic pesticides, is not tenable. Carcinogens occurring naturally in plants (for example, aflatoxins) may not be ignored, but it is well known that vegetarians have a considerably lower cancer risk than do omnivorous humans. There is a danger in turning over custody of our health to those who profess more knowledge than they possess. My apprehensions about fellow scientists with such a mind-set are expressed in the following short letter which I recently submitted to the magazine Science in response to a much longer letter from T.H. Jukes, ridiculing our apprehensions about exposure to commercial agricultural chemicals that are carcinogens. Science would not publish my letter, but it speaks for itself.

May 12, 1989

The Editor, SCIENCE

Thomas Jukes (Letters, 5 May, p. 515) has a point, that the assessment of risk in exposure to Alar (daminozide) by the National Resources Defense Council is arguable. What is not arguable is that unsymmetrical dimethylhydrazine (UDMH) formed from daminozide is a carcinogen, and daminozide is a commercial agricultural chemical leaving residues in apples. UDMH is weaker than the extremely potent dimethylnitrosamine in the species in which both were tested, but our limited knowledge of carcinogenesis does not permit us to estimate their relative potencies in humans. The Delaney Amendment requires that Alar be banned from human food, because it has been shown by appropriate tests to cause cancer in man or animals. The exposures of humans to Alar and UDMH might be small, but neither Dr. Jukes nor anyone else knows how to establish a threshold for exposure to carcinogens, the effects of which accumulate over time with results that we cannot measure or estimate. Of course, exposure to "natural" carcinogens is also important in the process, whether we can do anything about them (e.g. natural radiation) or not. However, both Dr. Jukes and the Ames article he quotes (1) introduce highly questionable animal testing data with natural substances as "evidence" that commercial carcinogens can be ignored. For example, three tests of patulin have been published (2) and not one shows evidence of carcinogenicity, yet Jukes calls it a suspected carcinogen; there is no such doubt about Alar and UDMH. That Ames *et al*. rank one mushroom as equivalent in hazard to the aflatoxin in three peanut butter sandwiches does not make it so, when the hydrazine-in-mushroom test (3) is so dubious that it would be unacceptable as evidence of carcinogenicity if it were a synthetic chemical.

William Lijinsky

(1) B.N. Ames, R. Magaw, L.S. Gold. Science 236, 271 (1987).
(2) U.S. Public Health Service Publication No. 149, Survey Of Compounds Which Have Been Tested For Carcinogenic Activity, 1961-67 Volume, 1978 Volume, 1981-82 Volume.
(3) B. Toth, J. Erickson. Cancer Res. 46, 4007, 1986.

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Dr. **Keith**. Thank you very much. We will be submitting questions for all of the witnesses for the record. You will have one week to reply.

At this time, we will have to end the hearing. We very much appreciate everyone coming today, especially those from out of town. Thank you.

[Whereupon, at 11:45 a.m., the committee was adjourned, subject to the call of the Chair.]

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